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(54) Title: STEM CELL

(57) Abstract: There is provided a method to modulate the differentiation state of embryonic stem cells in culture by the providing

WO 02/077204 A2

## STEM CELL

The invention relates to a method to modulate the differentiation state of embryonic stem cells.

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During mammalian development those cells that form part of the embryo up until the formation of the blastocyst are said to be totipotent (e.g. each cell has the developmental potential to form a complete embryo and all the cells required to support the growth and development of said embryo). During the formation of the  
10 blastocyst, the cells that comprise the inner cell mass are said to be pluripotential (e.g. each cell has the developmental potential to form a variety of tissues).

Embryonic stem cells (ES cells, those with pluripotentiality) may be principally derived from two embryonic sources. Cells isolated from the inner cell mass are  
15 termed embryonic stem (ES) cells. In the laboratory mouse, similar cells can be derived from the culture of primordial germ cells isolated from the mesenteries or genital ridges of days 8.5-12.5 *post coitum* embryos. These would ultimately differentiate into germ cells and are referred to as embryonic germ cells (EG cells). Each of these types of pluripotential cell has a similar developmental potential with  
20 respect to differentiation into alternate cell types, but possible differences in behaviour (eg with respect to imprinting) have led to these cells to be distinguished from one another. Hereinafter embryonic stem cells will encompass both these stem cell - types.

25 Typically ES cell cultures have well defined characteristics. These include, but are not limited to; maintenance in culture for at least 20 passages when maintained on fibroblast feeder layers; produce clusters of cells in culture referred to as embryoid bodies; the ability to differentiate into multiple cell types in monolayer culture; and express ES cell specific markers.

30

Until very recently, *in vitro* culture of human ES cells was not possible. The first indication that conditions may be determined which could allow the establishment of human ES cells in culture is described in WO96/22362. The application describes  
5 cell lines and growth conditions which allow the continuous proliferation of primate ES cells which exhibit a range of characteristics or markers which are associated with stem cells having pluripotent characteristics.

More recently Thomson *et al* (1998) have published conditions in which human ES  
10 cells can be established in culture. The above characteristics shown by primate ES cells are also shown by the human ES cell lines. In addition the human cell lines show high levels of telomerase activity, a characteristic of cells which have the ability to divide continuously in culture in an undifferentiated state. Another group (Reubinoff *et. al.*, 2000) have also reported the derivation of human ES cells from  
15 human blastocysts. A third group (Shamblott *et. al.*, 1998) have described EG cell derivation.

A feature of ES cells is that, in the presence of fibroblast feeder layers, they retain the ability to divide in an undifferentiated state for several generations. If the feeder  
20 layers are removed then the cells differentiate. The differentiation is often to neurones or muscle cells but the exact mechanism by which this occurs and its control remain unsolved. It would be desirable to have a reliable culture system which does not require the presence of fibroblast feeder cells but includes the addition of a factor(s) which maintain ES cells in an undifferentiated state. A  
25 prerequisite to the successful exploitation of ES cells in tissue engineering is to provide a reliable and defined cell culture system which can be used to control the differentiation of ES cells into a selected cell-type. The identification of gene targets involved in maintaining ES cells as ES cells and the identification of gene targets involved in differentiation will facilitate this objective.

30

We have identified a regulatory pathway involved in the mechanism by which ES cells are maintained as ES cells in culture and which also influences the differentiation of said cells in culture. The regulatory pathway comprises two families of genes referred to as *Notch* and *Wnt*.

5

The *Notch* gene is a *Drosophila* prototype for a family of homologues found in diverse species, encoding large, single-span, transmembrane receptors (reviewed in Weinmaster, 1997). Within the extracellular domain, located distally from the transmembrane region, are found multiple (10-36); tandem arrays of epidermal growth factor-like repeats (Wharton et al., 1985; Kopezynski et al., 1988). More proximally are found 3 cysteine-rich, Lin-12/Notch repeats and two conserved cysteine residues. The intracellular domain contains, from proximal to distal with respect to the transmembrane region, a subtransmembrane region (STR), six ankyrin repeats and a region rich in proline, glutamic acid, serine and threonine (PEST). The generic Notch structure is illustrated in Figure 1.

15

*Wnt* genes encode diffusible, extracellular signalling molecules of around 350-400 amino acids in length, defined by a characteristic pattern of conserved cysteine residues, along with other invariant amino acids (see <http://www.stanford.edu/~rnusse/wntwindow.html>).

20

In the 1970s, the *wingless* (*wg*<sup>1</sup>) mutation of *Drosophila melanogaster* was described, in which affected individuals showed aberrant wing and haltere development (Sharma, 1973; Sharma and Chopra, 1976). When the gene disrupted by this mutation was subsequently identified, the predicted 468aa peptide sequence exhibited remarkable similarity to that of a murine gene, *int-1* (Cabrera et al., 1987; Rijsewijk et al., 1987), including an identical pattern of 23 conserved cysteine residues. *int-1* had earlier been identified as a common integration site of the murine mammary tumour virus, and a likely cellular oncogene (Nusse and Varmus, 1982; van Ooyen and Nusse, 1984). Thus, the two prototypic members of the *Wnt* gene family were described. Since that time, numerous homologues of *wingless/int-1* have

30



been identified in divergent organisms, including *Caenorhabditis elegans*, *Drosophila melanogaster*, *Xenopus laevis*, chicken, mouse and humans (reviewed in Cadigan and Nusse, 1997; Wodarz and Nusse, 1998). Lower organisms appear to possess a limited repertoire of *Wnt* genes in comparison to higher organisms, presumably reflecting their lesser developmental complexity. Additionally, vertebrates appear to express multiple, closely related orthologues of certain *Wnts*. The *Wnt* family is composed of more than 60 members, with 14 human homologues alone. Well-documented roles exist for *Wnt* signalling in a variety of developmental processes, including cell fate specification and patterning within the central nervous system.

Wnt ligands interact with membrane-bound receptors of the frizzled family, leading to activation of a cytoplasmic protein, Dishevelled. Dishevelled inhibits Notch activation (2) and also inhibits the activity of an Axin-APC-GSK-3 $\beta$  complex, promoting formation of a bipartite transcriptional activator comprising b-catenin and TCF (4). Wnt signalling may be antagonised by extracellular molecules that compete for Wnt binding, including frizzled related proteins (FRP), Wnt inhibitory factors (WIF), Dickkopf and Cerberus. Expression of *Wnt* target genes may also be regulated by other proteins that bind to and alter the function of TCF. CREB-Binding Protein (CBP) exhibits a mutually antagonistic binding affinity for TCF with b-catenin and converts TCF into a repressor of target genes (8). Additionally, Notch activation may induce transcriptional repression by TCF, even in the presence of b-catenin, through expression of the TLE class of putative target genes (5,7).

As a model system to test the involvement of *Notch* and *Wnt* genes in the differentiation of ES cells we have used embryonal carcinoma cells which are stem cells of teratocarcinomas. The stem cells of early embryos and the stem cells of teratocarcinomas have been demonstrated experimentally to be capable of substituting for one another in their respective roles. Thus, an embryonic stem cell introduced to a syngeneic host may give rise to a teratocarcinoma containing all of the elements that would be found in a spontaneous tumour of this type (Mintz et al

1978). Likewise, embryonal carcinoma cells derived from a spontaneous germ cell carcinoma may participate in embryonic development, and generate normal somatic tissue following injection into a blastocyst (Brinster 1974; Mintz and Illmensee 1975; Papaioannou et al 1975). This clearly demonstrates that murine EC cells may respond  
5 to developmental cues in an appropriate manner, and that their differentiation may provide information pertinent to normal embryogenesis. Similarly, human EC cells may provide an insight into the processes that regulate human development.

The TERA2 cell line was derived from a lung metastasis of a human teratocarcinoma  
10 in the mid 1970s (Fogh and Trempe, 1975). Morphologically, TERA2 cultures are quite divergent from the characteristic EC phenotype and display significant heterogeneity, suggesting that these cells undergo spontaneous differentiation (Andrews et al., 1980). However, a tumour containing both embryonal carcinoma cells and differentiated derivatives was produced following injection of TERA2 into  
15 a nude mouse host (Andrews et al., 1983a; Andrews et al., 1983b; Andrews et al., 1984). A cell line established from the EC component of this tumour, named NTERA2, closely resembled and maintained the characteristic EC phenotype in culture and, unlike the parent line, was able to produce teratocarcinoma in nude mice with high frequency (Andrews et al., 1983a; Andrews et al., 1983b; Andrews et al.,  
20 1984). Additionally, various subclones of NTERA2 exhibit the ability to differentiate extensively *in vitro* following treatment with chemical inducers (eg retinoic acid (RA), HMBA ) (Andrews, 1984; Andrews et al., 1986).

The expression of human *Notch* homologues were examined in NTERA2 to  
25 determine their involvement in ES cell differentiation.

We have discovered that members of the *Notch* gene family, *Notch1* (Genbank accession number AF308602), *Notch2* (Genbank accession number NM\_024408) and *Notch3* (Genbank accession number NM\_000435) are expressed in EC cells and  
30 NTERA2 cells. *Notch1* expression was detected as a mRNA band of around 7Kb in both EC and differentiated cultures of NTERA2. *Notch3*, like *Notch1*, was

examined in EC cells. A transcript of around 8Kb was readily detected in all samples. The endoderm-specific *Notch4* (Genbank accession number XM\_004207) was not.

5 All three *Notch* homologues expressed by NTERA2 showed altered transcription during differentiation in response to retinoic acid. In each case, however, these changes were modest and expression was evident in both EC and differentiated cultures. The role of the Notch pathway in directing EC/ES differentiation may thus depend to a greater extent on the level of signalling activation rather than the abundance of the receptors. In order to investigate this possibility, the expression of  
10 candidate ligands for Notch receptors were examined. For example, *dlk* (Genbank accession number U15979) was detected at high levels in EC cultures, but its expression was almost extinguished by 3 days following RA treatment. Low levels were also observed through 7 and 14 days post-RA. However, by 21 days, *dlk* was up-regulated to the level seen in EC cultures. These profound changes may reflect an  
15 important role for *dlk* and other DSL ligands in regulating EC/ES differentiation through altered Notch signalling activation. This data is suggestive that the *Notch* signalling pathway is involved in regulating EC cell differentiation and, by extrapolation, human ES cell differentiation.

20 A degenerate PCR strategy was used to investigate the possible expression of novel *Wnt* genes in the NTERA2 system. The expression of a single *Wnt* gene, *Wnt-13*, was detected in NTERA2. *Wnt-13* was absent in EC cells, but showed induction and subsequent up-regulation following both retinoic acid and HMBA treatment. Both of these agents bring about extensive differentiation of NTERA2, accompanied by the  
25 loss of typical human EC surface markers.

We have examined the expression of components of the *Wnt* pathway and of transcripts corresponding to other proteins known to interact with *Wnt* signalling in NTERA2 cells. These cells are a model system for aspects of human embryogenesis  
30 and differentiate extensively *in vitro* in response to chemical inducers. Among the

cell types produced following retinoic acid treatment are functional, post-mitotic, CNS neurons (1,6,17).

5 The modulation of the *Notch* and *Wnt* signalling pathways may facilitate manipulation of embryonic stem cell differentiation. The term modulation refers to either the maintenance of embryonic stem cells as embryonic stem cells or the facilitation of differentiation of embryonic stem cells along defined cell lineages.

10 According to an aspect of the invention there is provided a method to modulate the phenotype of an embryonic stem cell comprising contacting said cell with a ligand binding domain of a polypeptide wherein said domain binds its cognate receptor expressed by said cell to modulate said phenotype.

15 According to a further aspect of the invention there is provided a method to modulate the differentiation of an embryonic stem cell comprising:

- i) providing a culture of embryonic stem cells;
- ii) providing at least one ligand, or the active binding fragment thereof, capable of binding its cognate receptor polypeptide expressed by said embryonic stem cell;
- 20 iii) forming a culture comprising embryonic stem cells and said ligand; and
- iv) growing said cell culture.

In a preferred method of the invention said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

- 25 i) a nucleic acid molecule as represented in Figure 22;
- ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of binding a Wnt receptor; and
- iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

In a preferred method of the invention said ligand is selected from the group consisting of: WNT 1; WNT 2; WNT 3; WNT 4; WNT 5A; WNT 6; WNT 7A; WNT 8B; WNT 10B; WNT 11; WNT 14; WNT 16.

5 In a further preferred method of the invention said ligand is WNT 13.

In an alternative preferred method of the invention said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

- 10 i) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, or 18.
- ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
- 15 iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

In a further preferred method of the invention said ligand is selected from the group represented by the amino acid sequences in Figures 3, 6, 8, 9, 11, 13, 15, 17, 19, or polypeptide variants thereof.

20

Polypeptide variants are polypeptide sequences having at least 75% identity with the polypeptide sequences as herein disclosed, or fragments and functionally equivalent polypeptides thereof. In one embodiment, the polypeptides have at least 85% identity, more preferably at least 90% identity, even more preferably at least 95% identity, still  
25 more preferably at least 97% identity, and most preferably at least 99% identity with the amino acid sequences illustrated herein.

In a further preferred method of the invention said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic  
30 acid; HMBA ; bone morphogenetic proteins ; bromodeoxyuridine; lithium; sonic hedgehog.

Optionally the inducing agent and the ligand are added simultaneously to a culture of embryonic stem cells. Alternatively, the ligand is added before addition of said inducing agent.

5 According to a further aspect of the invention there is provided a method for modulating the differentiation of embryonic stem cells comprising:

- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
  - a) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, 18.
  - 10 b) a nucleic acid molecule which hybridises to the nucleic acid in (ii) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
  - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- ii) forming a culture comprising the cell identified in (i) above with an  
15 embryonic stem cell; and
- iii) growing said culture under conditions suitable for the maintenance and/or differentiation of said embryonic stem cell.

According to a yet further aspect of the invention there is provided a method for  
20 modulating the differentiation of embryonic stem cells comprising:

- i) providing a cell transfected with a nucleic acid molecule selected from the group comprising:
  - a) a nucleic acid molecule as represented by the sequence in Figure 22;
  - b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and  
25 which encodes a ligand capable of binding a Wnt receptor; and
  - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- ii) forming a culture comprising a cell as identified in (i) above with an embryonic stem cell; and
- 30 iii) growing said culture under conditions suitable for the maintenance and/or differentiation of embryonic stem cells.

In a preferred method of the invention said cell expresses Wnt-13.

Optionally the cells expressing the ligand(s) are mixed with a culture of  
5 undifferentiated embryonic stem cells. This is followed by addition of the inducing  
agent ( eg retinoic acid; HMBA, bone morphogenetic proteins; bromodeoxyuridine;  
lithium; sonic hedgehog).

In a preferred method of the invention said nucleic acid molecule hybridises under  
10 stringent hybridisation conditions to the nucleic acid molecules represented in (a), (b)  
or (c) above.

Stringent hybridisation or washing conditions are well known in the art. For example,  
nucleic acid hybrids that are stable after washing in 0.1xSSC, 0.1% SDS at 60°C. It is  
15 well known in the art that optimal hybridisation conditions can be calculated if the  
sequence of the nucleic acid is known. For example, hybridisation conditions can be  
determined by the GC content of the nucleic acid subject to hybridisation. Please see  
Sambrook *et al* (1989) Molecular Cloning; A Laboratory Approach. A common  
formula for calculating the stringency conditions required to achieve hybridisation  
20 between nucleic acid molecules of a specified homology is:

$$T_m = 81.5^{\circ} \text{C} + 16.6 \log [\text{Na}^+] + 0.41 [\% \text{G} + \text{C}] - 0.63 (\% \text{formamide})$$

25 In a further preferred method of the invention the nucleic acid molecule is genomic  
DNA or cDNA.

In a preferred method of the invention the nucleic acid molecule encodes a ligand of  
human origin.

30

In a further preferred method of the invention said embryonic stem cells are of human  
origin.

In a yet further preferred method of the invention the cell transfected with the nucleic acid according to the invention is a mammalian cell. Preferably the cell is selected from the following group: a chinese hamster ovary cell; murine primary fibroblast cell; human primary fibroblast cell; transformed mouse fibroblast cell-line STO.

According to a further aspect of the invention there is provided a method for inhibiting the differentiation of embryonic stem cells or embryonal carcinoma cells comprising:

10

- i) providing at least one polypeptide, or active fragment thereof, wherein said polypeptide is an inhibitor of the *Wnt* signalling pathway.
- ii) forming a culture comprising the polypeptide identified in (i) above with an embryonic stem cell; and
- 15 iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

In a preferred method of the invention said inhibitor of Wnt signalling is selected from the group comprising the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); 20 Dickkopf; Cerebrus.

In a further preferred method of the invention said inhibitor of Wnt signalling is selected from the group comprising the active binding fragments thereof of the following polypeptides: SFRP1; SFRP4; FRZB; SFRP2; FZD1; FZD2; FZD9; FZD3; 25 FZD5; FZD4; FZD6; FZD7; DVL2; DVL3; GSK3B; AXIN1; APC; TCF1; WIF-1; CER 1; DKK1-4; SARP 2; SARP 3.

According to a further aspect of the invention there is provided a method for inhibiting the differentiation of embryonic stem cells or embryonal carcinoma cells 30 comprising:



- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
  - a) a nucleic acid molecule encoding a Wnt inhibitory polypeptide;
  - 5 b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a polypeptide capable of inhibiting *Wnt* signalling; and
  - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- ii) contacting the cell of (i) above with a culture of embryonic stem cells; and
- 10 iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

In a preferred method of the invention said cells express at least one Wnt inhibitory polypeptide selected from the group comprising the active binding fragments thereof  
15 of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus. Preferably said cells express at least one Wnt inhibitory polypeptide selected from the group comprising the active binding fragments thereof of the following polypeptides: SFRP1; SFRP4; FRZB; SFRP2; FZD1; FZD2; FZD9; FZD3; FZD5; FZD4; FZD6; FZD7; DVL2; DVL3; GSK3B;  
20 AXIN1; APC; TCF1; WIF-1; CER-1; DKK1-4

In a further preferred method of the invention the nucleic acid molecule is encoded by a nucleic acid molecule which hybridises under stringent hybridisation conditions to the nucleic acid molecules represented in (a), (b) or (c) above. Preferably said  
25 inhibitors are human.

According to a further aspect of the invention there is provided a vector comprising the nucleic acid molecule according to the invention. Preferably the vector is an expression vector adapted for the expression of the polypeptide encoded by said  
30 nucleic acid molecule.

Typically said adaptation includes, by example and not by way of limitation, the provision of transcription control sequences (promoter sequences) which mediate cell/tissue specific expression. These promoter sequences may be cell/tissue specific, inducible or constitutive.

5

Promoter is an art recognised term and, for the sake of clarity, includes the following features which are provided by example only, and not by way of limitation. Enhancer elements are *cis* acting nucleic acid sequences often found 5' to the transcription initiation site of a gene (enhancers can also be found 3' to a gene sequence or even

10 located in intronic sequences and is therefore position independent). Enhancers function to increase the rate of transcription of the gene to which the enhancer is linked. Enhancer activity is responsive to *trans* acting transcription factors (polypeptides) which have been shown to bind specifically to enhancer elements. The binding/activity of transcription factors (please see Eukaryotic Transcription Factors, 15 by David S Latchman, Academic Press Ltd, San Diego) is responsive to a number of environmental cues which include, by example and not by way of limitation, intermediary metabolites (eg glucose, lipids), environmental effectors (eg light, heat,).

20 Promoter elements also include so called TATA box and RNA polymerase initiation selection (RIS) sequences which function to select a site of transcription initiation. These sequences also bind polypeptides which function, *inter alia*, to facilitate transcription initiation selection by RNA polymerase.

25 Adaptations also include the provision of selectable markers and autonomous replication sequences which both facilitate the maintenance of said vector in either the eukaryotic cell or prokaryotic host. Vectors which are maintained autonomously are referred to as episomal vectors. Episomal vectors are desirable since these molecules can incorporate large DNA fragments (30-50kb DNA). 30 Episomal vectors of this type are described in WO98/07876. Alternatively, the vector is an integrating vector.

Adaptations which facilitate the expression of vector encoded genes include the provision of transcription termination/polyadenylation sequences. This also includes the provision of internal ribosome entry sites (IRES) which function to maximise expression of vector encoded genes arranged in bicistronic or multi-cistronic expression cassettes.

These adaptations are well known in the art. There is a significant amount of published literature with respect to expression vector construction and recombinant DNA techniques in general. Please see, Sambrook et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory, Cold Spring Harbour, NY and references therein; Marston, F (1987) DNA Cloning Techniques: A Practical Approach Vol III IRL Press, Oxford UK; DNA Cloning: F M Ausubel et al, Current Protocols in Molecular Biology, John Wiley & Sons, Inc.(1994).

Conventional methods to introduce DNA or vector DNA into cells are well known in the art and typically involve the use of chemical reagents, cationic lipids or physical methods. Chemical methods which facilitate the uptake of DNA by cells include the use of DEAE -Dextran ( Vaheri and Pagano Science 175: p434) . DEAE-dextran is a negatively charged cation which associates and introduces the DNA into cells but which can result in loss of cell viability. Calcium phosphate is also a commonly used chemical agent which when co-precipitated with DNA introduces the DNA into cells (Graham et al Virology (1973) 52: p456).

The use of cationic lipids (eg liposomes, Felgner (1987) Proc.Natl.Acad.Sci USA, 84:p7413) has become a common method since it does not have the degree of toxicity shown by the above described chemical methods. The cationic head of the lipid associates with the negatively charged nucleic acid backbone of the DNA to be introduced. The lipid/DNA complex associates with the cell membrane and fuses with the cell to introduce the associated DNA into the cell. Liposome mediated DNA transfer has several advantages over existing methods. For example, cells which are

recalcitrant to traditional chemical methods are more easily transfected using liposome mediated transfer.

5 More recently still, physical methods to introduce DNA have become effective means to reproducibly transfect cells. Direct microinjection is one such method which can deliver DNA directly to the nucleus of a cell (Capecchi (1980) Cell, 22:p479). This allows the analysis of single cell transfectants. So called "biolistic" methods physically shoot DNA into cells and/or organelles using a particle gun (Neumann (1982) EMBO J, 1: p841). Electroporation is arguably the most popular method to  
10 transfect DNA. The method involves the use of a high voltage electrical charge to momentarily permeabilise cell membranes making them permeable to macromolecular complexes. However physical methods to introduce DNA do result in considerable loss of cell viability due to intracellular damage. These methods therefore require extensive optimisation and also require expensive equipment.

15

More recently still a method termed immunoporation has become a recognised technique for the introduction of nucleic acid into cells, see Bildirici et al, Nature 405, 769. The technique involves the use of beads coated with an antibody to a specific receptor. The transfection mixture includes nucleic acid, typically vector  
20 DNA, antibody coated beads and cells expressing a specific cell surface receptor. The coated beads bind the cell surface receptor and when a shear force is applied to the cells the beads are stripped from the cell surface. During bead removal a transient hole is created through which nucleic acid and/or other biological molecules, eg polypeptides, can enter. Transfection efficiency of between 40-50% is achievable  
25 depending on the nucleic acid used.

Other non-liposome based, chemical transfectant agents have become available, for example ExGen500 (polyethylenimine), produced by MBI Fermentas. ExGen500 is particularly effective for transfection of human ES cells (Eiges, 2001).

30

According to a further aspect of the invention there is provided a method for the production of the polypeptide encoded by the nucleic acid molecule according to the invention comprising:

- 5 i) providing a cell transformed/transfected with a nucleic acid molecule according to the invention;
- ii) growing said cell in conditions conducive to the manufacture of said polypeptide; and
- i) purifying said polypeptide from said cell, or its growth environment.

10 In a preferred method of the invention said nucleic acid molecule is the vector according to the invention.

In a further preferred method of the invention said vector encodes, and thus said recombinant polypeptide is provided with, a secretion signal to facilitate purification of said polypeptide.

15

According to a further aspect of the invention there are provided host cells which have been transformed/transfected with the vector according to the invention, so as to include at least part of the polypeptide according to the invention, so as to permit expression of at least the functional part of the polypeptide encoded by said nucleic acid molecule.

20

Ideally said host cells are eukaryotic cells, for example, insect cells such as cells from a species *Spodoptera frugiperda* using the baculovirus expression system.

25 According to a further aspect of the invention there is provided a therapeutic cell composition comprising differentiated or differentiating embryonic stem cells derived by the method according to the invention. Preferably said composition is for

use in the treatment of: Parkinson's disease; Huntington's disease; motor neurone disease; heart disease; diabetes; liver disease (eg cirrhosis); renal disease; AIDS.

According to a further aspect of the invention there is provided a method of treatment  
5 of an animal comprising administering a cell composition comprising embryonic stem cells which have been induced to differentiate into at least one cell-type.

According to a yet further aspect of the invention there is provided condition medium  
10 obtained by culturing embryonic stem cells according to any of the methods hereindisclosed.

An embodiment of the invention will now be described by example only and with reference to the following figures:

15 Figure 1 is a schematic representation of conserved domains in Notch polypeptides;

Figure 2 is the nucleic acid sequence of murine notch ligand delta-like 1;

Figure 3 is the amino acid sequence of murine notch ligand delta-like 1;

20

Figure 4 is the nucleic acid sequence of murine notch ligand jagged 1;

Figure 5 is the nucleic acid sequence of human notch ligand jagged 1 (alagille syndrome) (JAG1);

25

Figure 6 is the amino acid sequence of human notch ligand jagged 1 (alagille syndrome);

Figure 7 is the nucleic acid sequence of human notch ligand jagged 2 (JAG2)

30

Figure 8 is the amino acid sequence of human notch ligand jagged 2 (JAG2);

Figure 9 is the amino acid sequence of murine notch ligand jagged 1;

Figure 10 is the nucleic acid sequence of murine notch ligand jagged 2;

5

Figure 11 is the amino acid sequence of murine notch ligand jagged 2;

Figure 12 is the nucleic acid sequence of human notch ligand delta-like 3 (DLL3);

10 Figure 13 is the amino acid sequence of human notch ligand delta-like 3 precursor polypeptide;

Figure 14 is the nucleic acid sequence of human notch ligand delta-1 (DLL1);

15 Figure 15 is the amino acid sequence of murine notch ligand delta-like 1;

Figure 16 is the nucleic acid sequence of human notch ligand delta-like 4 (DLL4);

Figure 17 is the amino acid sequence of human notch ligand delta-like 4 (DLL4);

20

Figure 18 is the nucleic acid sequence of murine notch ligand delta-like 4 (DLL4);

Figure 19 is the amino acid sequence of murine notch ligand delta-like 4 (DLL4);

25 Figure 20 is a western blot of cell extracts of various EC cell-lines probed with Notch 2 antisera;

Figure 21 represents northern blot analysis of the expression patterns of notch genes (*Notch 1,2,3*) and notch ligands (*Dlk, jagged 1*) in EC cells and EC cells treated with

30 retinoic acid (RA);

Figure 22 represents the nucleic acid sequence of human *Wnt 13*;

Figure 23 is a diagrammatic representation of the Wnt signalling pathway;

- 5    Figure 24 represents northern blot analysis of *Wnt 13* and mRNA's corresponding to Frizzled receptors and Frizzled related protein antagonists of Wnt signalling in NTERA 2 cells various Wnt inhibitors after exposure of NTERA 2 cells;

- 10   Figure 25 represents a northern blot analysis of intracellular components of Wnt signalling pathway in NTERA 2 cells;

Figure 26 represents the nucleic acid sequence of human *dickkopf1*;

Figure 27 represents the nucleic acid sequence of human *dickkopf2*;

15

Figure 28 represents the nucleic acid sequence of human *dickkopf3*; and

Figure 29 represents the nucleic acid sequence of human *dickkopf4*;

- 20   Figure 30 represents the nucleic acid sequence of WNT-1;

Figure 31 represents the amino acid sequence of WNT-1;

Figure 32 represents the nucleic acid sequence of WNT-2;

25

Figure 33 represents the amino acid sequence of WNT-2;

Figure 34 represents the nucleic acid sequence of WNT 2B;

- 30   Figure 35 represents the amino acid sequence of WNT 2B;



- Figure 36 represents the nucleic acid sequence of WNT 3;
- Figure 37 represents the amino acid sequence of WNT 3;
- 5 Figure 38 represents the nucleic acid sequence of WNT 4;
- Figure 39 represents the amino acid sequence of WNT 4;
- Figure 40 represents the nucleic acid sequence of WNT 5A;
- 10 Figure 41 represents the amino acid sequence of WNT 5A;
- Figure 42 represents the nucleic acid sequence of WNT 6;
- 15 Figure 43 represents the amino acid sequence of WNT 6;
- Figure 44 represents the nucleic acid sequence of WNT 7A;
- Figure 45 represents the amino acid sequence of WNT 7A;
- 20 Figure 46 represents the amino acid sequence of WNT 7B;
- Figure 47 represents the nucleic acid sequence of WNT 8B;
- 25 Figure 48 represents the amino acid sequence of WNT 8B;
- Figure 49 represents the nucleic acid sequence of WNT 10B;
- Figure 50 represents the amino acid sequence of WNT 10B;
- 30 Figure 51 represents the nucleic acid sequence of WNT 11;

Figure 52 represents the amino acid sequence of WNT 11;

Figure 53 represents the nucleic acid sequence of WNT 14

5

Figure 54 represents the amino acid sequence of WNT 14;

Figure 55 represents the nucleic acid sequence of WNT 16;

10 Figure 56 represents the amino acid sequence of WNT 16;

Figure 57 represents the nucleic acid sequence of FZD 1;

Figure 58 represents the amino acid sequence of FZD 1;

15

Figure 59 represents the nucleic acid sequence of FZD 2;

Figure 60 represents the amino acid sequence of FZD 2;

20 Figure 61 represents the nucleic acid sequence of FZE 3;

Figure 62 represents the amino acid sequence of FZE 3;

Figure 63 represents the nucleic acid sequence of FZD 4;

25

Figure 64 represents the amino acid sequence of FZD 4;

Figure 65 represents the nucleic acid sequence of FZD 5;

30 Figure 66 represents the amino acid sequence of FZD 5;

- Figure 67 represents the nucleic acid sequence of FZD 6;
- Figure 68 represents the amino acid sequence of FZD 6;
- 5 Figure 69 represents the nucleic acid sequence of FZD 7;
- Figure 70 represents the amino acid sequence of FZD 7;
- Figure 71 represents the nucleic acid sequence of FZD 8;
- 10 Figure 72 represents the amino acid sequence of FZD 8;
- Figure 73 represents the nucleic acid sequence of FZD 9;
- 15 Figure 74 represents the amino acid sequence of FZD 9;
- Figure 75 represents the nucleic acid sequence of FZD 10;
- Figure 76 represents the amino acid sequence of FZD 10;
- 20 Figure 77 represents the nucleic acid sequence of FRP;
- Figure 78 represents the amino acid sequence of FRP;
- 25 Figure 79 represents the nucleic acid sequence of SARP 1;
- Figure 80 represents the amino acid sequence of SARP 1;
- Figure 81 represents the nucleic acid sequence of SARP 2;
- 30 Figure 82 represents the amino acid sequence of SARP 2;

Figure 83 represents the nucleic acid sequence of FRZB;

Figure 84 represents the amino acid sequence of FRZB;

5 Figure 85 represents the nucleic acid sequence of FRPHE;

Figure 86 represents the amino acid sequence of FRPHE;

Figure 87 represents the nucleic acid sequence of SARP 3;

10

Figure 88 represents the amino acid sequence of SARP 3;

Figure 89 represents the nucleic acid sequence of CER 1;

15 Figure 90 represents the amino acid sequence of CER 1;

Figure 91 represents the nucleic acid sequence of DKK1;

Figure 92 represents the amino acid sequence of DKK1;

20

Figure 93 represents the nucleic acid sequence of DKK 2;

Figure 94 represents the amino acid sequence of DKK 2;

25 Figure 95 represents the nucleic acid sequence of DKK 3;

Figure 96 represents the amino acid sequence of DKK 3;

Figure 97 represents the nucleic acid sequence of DKK 4;

30 Figure 98 represents the amino acid sequence of DKK 4;

Figure 99 represents the nucleic acid sequence of WIF-1;

Figure 100 represents the amino acid sequence of WIF-1;

5 Figure 101 represents the nucleic acid sequence of SRFP 1;

Figure 102 represents the amino acid sequence of SRFP 1;

Figure 103 represents the nucleic acid sequence of SRFP 4;

10

Figure 104 represents the amino acid sequence of SRFP 4; and

Figure 105 represents a diagram depicting the pCMV-tracer vector.

## 15 Materials and Methods

**Table 1 Cell lines derived from germ cell tumours.**

Cell Line	Biopsy Site	Biopsy Histology	Xenograph Histology	Reference
2102Ep	Testis	EC, T, Y	EC	(Andrews <i>et al.</i> , 1980)
833KE	Testis	EC, T, C, S	EC	(Andrews <i>et al.</i> , 1980)
TERA-1	Lung	EC, T		(Fogh and Trempe, 1975)
NTERA2 cl. D1	Lung	EC, T	EC, T	(Fogh and Trempe, 1975) (Andrews, 1984)

Abbreviations used: EC, embryonal carcinoma, T, teratoma, S, seminoma, C, choriocarcinoma, Y, yolk-sac carcinoma

**Cell Lines derived from gestational choriocarcinomas.**

BEWO	Corresponds to gestational choriocarcinoma	(Patillo and Gay, 1968)
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**5 List of Antibodies Used**

Antibody	Reference	References
SSEA-3	Andrews et. al., 1982	12
SSEA-4	Kannagi et. al., 1983	18
Tra-1-60	Andrews et. al., 1984	25
Tra-1-81	Andrews et. al., 1984	25
Tra-2-54	Andrews et. al., 1984	20
Tra-2-49	Andrews et. al., 1984	20
A2B5	Fenderson et. al., 1987	
ME311	Fenderson et. al., 1987	
Vin-is-56	Andrews et. al., 1990	44
Vin-is-53	Andrews et. al., 1990	44
Vin-2PB-22	Andrews et. al., 1990	44
Thy-1	Andrews et. al., 1983	10

**Expression Vectors**

- 10 The following mammalian expression vectors are used in the expression of ligands hereindisclosed:

Purchased from Stratagene Inc. pExchange-1; pExchange-2; pExchange-3A, 3B, 3C; pExchange-4A, 4B, 4C; pExchange-5A, 5b, 5C; pExchange-6A, 6B, 6C; pExchange module EC-hyg; pExchange module EC-Puro; pExchange module EC-Neo; pCMV-

- 15 Script; pCMV-Tag1; pCMV-Tag2; pCMV-Tag3; pCMV-Tag4; pCMV-Tag5; pCMVLACI, pOPRSVI/MCS, pOPI3-CAT; pERV3; pEGSH.

Purchased from Invitrogen Inv.

**T-REX System vectors**

- 20 pcDNA4/TO; pcDNA4/TO/myc-His; pcDNA6/TR; pT-Rex-DEST30; pT-Rex-DEST31; pcDNA4/TO-E; pcDNA5/FRT/TO; pcDNA5/FRT/TO-TOPO.

**Geneswitch System vectors**

pGene/V5-His A, B, C; pSwitch

5 **Ecdysone-Inducible System**

PVgRXR; pIND; pIND(SP1); pIND/V5-His; pIND/V5-His-TOPO; pIND/GFP;  
pIND(SP1)/GFP.

10 **PShooter vectors**

pRF/Myc/Nuc; pCMV/Myc/nuc; pEF/myc/mito; pCMV/myc/mito; pEF/myc/ER;  
pCMV/myc/ER; pEF/myc/cyto; pCMV/myc/cyto.

15 **INVITROGEN INC**

pTet-off; pTet-on; pTA-2/ /3 /4; pTet-tTS; pTRE2hyg  
PTRE2pur; pTRE2; pLP-TRE2; PTRE-Myc; pTRE-HA; pTRE-6xHN  
pTRE-d2EGFP; pBI; pBI-EGFP; pBI-G; pBI-L; pTK-Hyg

20

**"Living colours" vectors.**

pDsRed2-N1; pDsRed2-C1; pECFP-N1; pEGFP-N1; pEGFP-N2; pEGFP-N3  
pEYFP-N1; pECFP-C1; pEGFP-C1; pEGFP-C2; pEGFP-C3  
25 pEYFP-C1; pd1EGFP-N1; pd1ECFP-N1; pd2EGFP-N1; pd2EYFP-N1  
pd4EGFP-N1; pCMS-EGFP; pHygEGFP; pEGFPLuc; pNF- $\kappa$ B-dsEGFP  
pIRES2-EGFP; pIRES-EYFP

**Maintenance of cell lines**

30

All cells were grown in Dulbecco's modified Eagle's medium (DMEM),  
supplemented with 10% by volume foetal calf serum (Gibco BRL) and 2mM L-  
glutamine. Tissue culture flasks were incubated in a humidified atmosphere of 10%  
CO<sub>2</sub> in air at 37°C.

35

### Treatment of NTERA2 Cells

#### Retinoic acid

- 5 Medium was aspirated from confluent flasks of EC cells and the cells rinsed in sterile PBS. 1ml of 0.25% (w/v) trypsin in 2mM EDTA was added per 75cm<sup>2</sup> flask and the flask incubated at room temperature for up to 5 minutes. Vigorous shaking was subsequently used to dislodge the cells. Cells were suspended in 9ml of supplemented DMEM per ml of trypsin used and counted in a haemocytometer. Cells
- 10 were seeded at 10<sup>6</sup> cells per 75cm<sup>2</sup> flask, in medium containing 10<sup>-5</sup>M all-*trans*-retinoic acid (Eastman Kodak), diluted from a 10<sup>-2</sup>M stock solution in dimethyl sulfoxide (DMSO). Flasks were incubated as described above and the media replaced as and when required.

#### 15 Hexamethylene bisacetamide (HMBA)

Cells to be treated with HMBA were prepared as described for retinoic acid, but grown in medium supplemented with 10<sup>-3</sup>M HMBA instead of RA.

#### Harvesting of cells

- 20 Cells were dislodged from the culture vessel with trypsin and suspended in 9ml culture medium per ml of trypsin solution used, as described above. The cell suspension was then centrifuged at 400 x g for 3 minutes and the medium aspirated from the resulting cell pellet. Cells were then rinsed in 5ml PBS and centrifuged again at 400 x g for 1 minute. The PBS rinse was aspirated and the cells stored at –
- 25 80°C or used immediately.

#### Total RNA preparation

- Where possible, all vessels and all solutions used in RNA preparation and storage
- 30 were treated with a 0.01% (v/v) solution of diethylpyrocarbonate (DEPC) in distilled water, and subsequently autoclaved.



TRI reagent (Sigma) was added to pelleted cells in a quantity corresponding to 1ml per 75cm<sup>2</sup> flask. The lysate was agitated until homogenous. 0.2ml of chloroform was added per ml of TRI reagent used and the vessel vortexed for 10 seconds. After 10 minutes at room temperature, the lysate was centrifuged at 12000 x g for 15 minutes at 4°C. Following centrifugation, the aqueous (uppermost) phase was transferred to a fresh vessel and 0.5ml of isopropanol added per ml of TRI reagent used. The sample was incubated at room temperature for 10 minutes, then centrifuged at 12000 x g for 10 minutes at 4°C. Following centrifugation, the supernatant was removed and the pellet washed in 70% ethanol. RNA was dissolved in DEPC-treated, double-distilled water.

#### Isolation of mRNA

100mg oligo dT cellulose (Ambion) was suspended in 25ml binding buffer. Up to 2mg of total RNA was then added to the binding buffer and the suspension gently agitated at room temperature for 45 minutes. The suspension was then centrifuged at 3000 x g for 10 minutes and the supernatant discarded. The resulting pellet was re-suspended in a further 25ml of binding buffer and agitated at room temperature for 60 minutes. The suspension was again centrifuged at 3000 x g and the supernatant discarded. The pellet of oligo dT cellulose was transferred to a spin column using a minimal quantity of binding buffer to re-suspend. The column was spun at maximum speed in a desktop microfuge for 30 seconds and the eluate discarded. This was repeated until the cellulose was dry. 200µl of wash buffer was then added to the cellulose and mixed in with a pipette tip. The column was spun at maximum speed for 1 minute and the eluate discarded. 200µl of DEPC-treated, double-distilled H<sub>2</sub>O was then added to the cellulose and mixed in, as before. The column was then spun at maximum speed for 2 minutes and the eluted mRNA collected.

#### Precipitation of RNA

To the RNA solution was added 0.1x volume of 5M LiCl and 2.5x volume of 100% ethanol. After vortexing briefly, the sample was incubated at -20°C for >60 minutes

to precipitate. Precipitated RNA was centrifuged at maximum speed in a bench top microfuge for 30 minutes. The supernatant was discarded and the pellet rinsed in 70% ethanol, then dissolved in H<sub>2</sub>O.

#### Quantitation of nucleic acid

5

A Beckman DU 650 spectrophotometer was used for the quantitation of both DNA and RNA. The machine was set to measure absorbance at wavelengths of 260nm and 280nm. After blanking the machine on an appropriate solution, diluted DNA or RNA samples in a volume of 100µl were added to the cuvette and measured. The  
10 absorbance at 260nm was used to calculate nucleic acid concentration in µg/µl, as shown below:

$$[\text{Nucleic acid}] = (A^{260} \times N \times \text{DF}) \div 1000$$

15 Where N is 33 for single-stranded DNA, 50 for double-stranded DNA and 40 for RNA and DF is the dilution factor for the sample added to the cuvette.

#### Northern blot analysis

##### Blot preparation

20 1g of agarose was dissolved in 85ml H<sub>2</sub>O by boiling. After cooling to around 70°C, 10ml of 10x MOPS buffer and 5ml of formaldehyde were added, and the gel cast. 1-5µg of each mRNA sample was mixed with an appropriate quantity of 10x RNA loading buffer to give a final volume of no more than 30µl. The RNA was then denatured at 95°C for 2 minutes and quenched on ice for 10 minutes. The gel was  
25 placed in an electrophoresis tank containing 1x MOPS buffer and the samples loaded into each well of the gel, along with appropriate molecular weight markers in the outermost wells. 80V were applied across the gel for 2-3 hours or as required. Following electrophoresis, the outermost lanes containing the molecular weight markers were removed using a scalpel and submerged in double-distilled H<sub>2</sub>O  
30 containing ethidium bromide at 0.5µg/ml. The remainder of the gel was submerged in >5 volumes of double-distilled H<sub>2</sub>O, which was replaced every 5 minutes for a total

of 25 minutes. An appropriately sized piece of GeneScreen Plus (DuPont) membrane, just larger than the area of gel to be blotted, was cut. The membrane was hydrated by briefly submerging in double-distilled H<sub>2</sub>O, then transferred to 10x SSC, concurrent with the last 15 minutes of gel washing. The blotting apparatus was assembled as shown in Figure 2.1, with the gel upside-down, using 10x SSC transfer buffer. After transfer of at least 6 hours, the absorbent material was removed from the membrane. After marking the position of the wells using a pencil, the membrane was removed from the gel and washed briefly in 2x SSC. Whilst still damp, the RNA was fixed to the membrane by UV crosslinking. The membrane was then baked at 80°C for 3 hours.

The excised marker lanes were de-stained by soaking in a large volume of double-distilled H<sub>2</sub>O for around 3 hours, after which they were visualised on a UV transilluminator and photographed.

15

### Probe preparation

Random-primed DNA labelling was carried out using the Prime-a-Gene kit from Promega. Approximately 25ng of template DNA (PCR or restriction digest product) was denatured at 95°C for 2 minutes, then quenched on ice for 10 minutes. The reaction mix was then assembled on ice, in the order indicated below:

- 10µl of 5x labelling buffer
- H<sub>2</sub>O to give a final volume of 50µl
- 2µl unlabelled dNTP mix (0.5mM each)
- 25ng of denatured/quenched template DNA
- 2µl 10mg/ml BSA
- 5µl αP<sup>32</sup> dATP 3000Ci/mmol (NEN DuPont)
- 1µl DNA polymerase 1 large (Klenow) fragment

30

The labelling reaction mix was incubated at room temperature for 2 hours. After this period, unincorporated nucleotides were removed using Pharmacia S-300 MicroSpin columns. Columns were placed in a microfuge tube and pre-spun at 735 x g for 1 minute. The column was then transferred to a fresh tube and the entire labelling reaction added. The column was then spun at 735 x g for a further 2 minutes and the purified, labelled DNA collected. Labelled DNA was denatured at 95°C for 2 minutes, then quenched on ice for 15 minutes.

#### Hybridisation and washing procedure

Northern blots were equilibrated in 150ml of 2x SSC at 42°C for 15 minutes in a hybridisation oven at 8 RPM. The SSC was exchanged for 25ml of hybridisation buffer, pre-warmed to 42°C, and the filter incubated for a further 30 minutes at the same temperature. The entire volume of purified probe solution was then added to the hybridisation buffer and the blot incubated overnight at 42°C/ 8 RPM. The hybridisation solution was then discarded and the blot washed as follows:

2x SSC at room temperature for 20 minutes  
2x SSC at room temperature for 20 minutes  
2x SSC/1% SDS at 65°C for 45 minutes  
2x SSC/1% SDS at 65°C for 45 minutes  
0.1x SSC at room temperature for 20 minutes  
0.1x SSC at room temperature for 20 minutes

Filters were exposed to a Bio Rad BI phosphor-imager screen overnight and, in most cases, subsequently exposed to X-ray film (Kodak X-omat AR).

#### Loading controls for Northern blots

All Northern blots used in this study were probed with  $\beta$ -actin as a loading control. Table 2.5 (overleaf) lists the figures to which each control probing (panel A to T, Figure 2.2) corresponds. Northern blot data presented in this study have not, in all

cases, been subject to repeat experiments using RNA isolated from different batches of cells. These data may not be regarded as conclusive, since reproducibility has not been proven.

5 **Method for Analysis of the Requirement for Notch Ligands in the Differentiation of Embryonic Stem, Embryonal Carcinoma and their Differentiated Derivatives.**

10 CHO are transfected with constructs encoding either membrane bound or soluble forms of the Notch ligands. These cell lines are used to support the growth of either Embryonal carcinoma cells (EC) e.g NTERA2/cl.D1 or Human embryonic stem cells (hES).

15 The transfected CHO cells (CHO(DSL)) are used in the following way. To assess membrane bound forms of the Notch ligands the CHO(DSL) cells are used as feeder cells (i.e. the EC or hES will be grown on top of the CHO(DSL) cells). To assess the soluble forms of the Notch ligands either supernatant from the transfected CHO cells or concentrated ligand molecules derived from the supernatant are added to the culture medium of the EC and hES cells.

20

**Notch Ligand Constructs.**

The following cloned Notch ligands were obtained from Dr. Shigeru Chiba, Department of Hematology, Oncology and Cell Therapy, Transplantation Medicine.  
25 Graduate School of Medicine. University of Tokyo.

Delta1-FLAG

Jagged1-FLAG

Jagged2-FLAG

30

Soluble Delta1-Fc

Soluble Jagged1-Fc

### Soluble Jagged2-Fc

These had been cloned into the vector pTRACER-CMV from Invitrogen, Fig 30).

- 5 The clones used consisted either of the full length ligand linked to a histidine tag (FLAG, Kodak Inc.), or a ligand lacking the membrane spanning and intracellular portion of the protein thus rendering the ligand soluble. These had been linked to the Fc portion of human IgG.

### 10 Generation of Notch Ligand expressing Cell lines

- The Chinese Hamster Ovary derived cell line AA8 was maintained in MEM Alpha medium with Glutamax-1 supplemented with ribonucleosides and deoxyribonucleosides (Lifetechnologies) and 10% Foetal Bovine Serum  
15 (FBS)(Lifetechnologies).

Plasmid was transfected into the AA8 cells using either Fugene (Roche) or Lipofectin (Lifetechnologies) or Superfect (Qiagen) according to manufacturers protocols.

### 20 Assessment of Transiently Transfected Cell lines for Ligand Production.

Both soluble and membrane bound forms of the Notch ligand's production are assayed by western blotting and chemiluminescent detection.

- 25 Cells transfected with the ligand encoding constructs are harvested and the proteins extracted. Due to the tagging of the ligands proteins are able to be run out on an SDS-PAGE gel, blotted and probed with either mouse anti-FLAG antibody and detected using a anti-mouse HRP secondary or an HRP-secondary antibody. Both methods use electro-chemiluminescence (ECL) as the detection method.

30

**Concentration of Soluble Notch ligand from the Supernatant of Transfected CHO cells.**

- 5 Fc-labelled Notch ligand can be purified from transfected CHO cells supernatant using a HiTrap protein G HP column (Amersham Pharmacia Biotech). A sample can be analysed by western blotting as described above.

**Embryonic Cell culture.**

- 10 Human Embryonal Carcinoma NTERA2/D1 cells are maintained in Dulbecco's modified Eagles medium (DMEM), supplemented with 2mM l-glutamine, 10% Foetal Bovine Serum (Lifetechnologies) and at 37°C under 10% CO<sub>2</sub> in air. Cells were passaged by scraping from the surface of the tissue culture flask with 3mm glass beads and reseeded at 5 x 10<sup>6</sup> cells per 75cm<sup>3</sup> flask. For specific seeding densities  
15 cells were passaged using 0.25% Trypsin (Lifetechnologies) in Dulbecco's Phosphate Buffered Saline (PBS) supplemented with 1mM EDTA.

- Human Embryonic Stem Cells are maintained on irradiated mouse embryonic fibroblasts in serum free conditions, with 80% F12:DMEM (Lifetechnologies), 20%  
20 Knockout SR (Lifetechnologies), 1% Non-essential amino acid solution (Lifetechnologies), 1 mM L-glutamine, 0.1mM β-mercaptoethanol (Sigma) 4 ng/ml bFGF (Sigma). The cells are passaged using collagenase IV and scraping.

**Flow Cytofluorimetry**

- 25 Cells were removed from their adherent culture surface and incubated with suitable primary antibody for 1 hour at 4C. Cells are washed in PBS with 5% FCS and incubated for a further hour with a suitable FITC-conjugated labelled secondary antibody, and analysed on a EPICS Elite ESP Flow Cytometer (Coulter Electronics). Colonies were assessed for the presence of embryonal stem cell markers such as  
30 SSEA-3, -4, Tra-1-60 and for appearance of markers of differentiated marker antigens such as A2B5, ME311 and N901.

### Design of oligonucleotide primers

Primers for use in PCR were designed on a Macintosh Power PC, using the "Primer Select" program of the DNASTAR software package (DNASTAR Inc.). All primers used in this study are shown in Table 2

**Table 2 List of oligonucleotide primers**

Gene	GenBank accession	Primer direction	Primer location	Primer sequence 5' to 3'
<i>Wnt-13</i>	Z71621	Forward	1159-1178	Tgagtgggtcctgtactctg
		Reverse	1503-1484	Actcacactgggtaacacgg
<i>SFRP4</i>	XM_004706	Forward	858-880	Agaggagtggctgcaatgaggct
		Reverse	1159-1142	Gcgcccggtgtttctt
<i>Waf1</i>	U03106	Forward	487-506	Cagggtcgaaaacggcggca
		Reverse	947-928	Aggagccacacccctccaga
$\beta$ -actin	NM_001101	Forward	326-357	Atctggcaccacaccttacaatgagctgc
		Reverse	1163-1132	Cgtcactactcctgctgtgatccacatctgc
<i>neuroD1</i>	NM_002500	Forward	240-263	Aagcatgaacgcagaggaggact
		Reverse	818-799	Agctgtccatggtaccgtaa

All PCR data presented in this study were duplicated in independent experiments to eliminate the possibility of methodological error. However, duplicate experiments were performed on identical samples and do not, therefore, control for variability between separate batches of cells. Polymerase chain reactions from which quantitative interpretations were to be made were controlled by parallel amplification of the cyclin-dependent kinase inhibitor, *Waf1*. This transcript has been demonstrated by other workers in the laboratory to be constitutively expressed by NTERA2 EC cells and differentiated derivatives (unpublished data). Furthermore, *Waf1* has been shown to exhibit an approximately 20-fold lower abundance in the NTERA2 system than the more widely used control,  $\beta$ -actin, and is therefore well suited to the analysis of rare transcripts.

### PCR Reaction conditions

PCR mixes were assembled on ice, with the following components per reaction:



- 5  
10
- 5µl of 25mM MgCl<sub>2</sub>
  - 5µl of 10x reaction buffer
  - 5µl of 1mM dNTPs
  - 3µl of forward primer at 5pmol/µl
  - 3µl of reverse primer at 5pmol/µl
  - 0.3µl of Taq polymerase at 1 unit/µl (Promega)
  - template and H<sub>2</sub>O to give 50µl final volume

10 A premix was made containing all reaction components bar the template. Premix was then added to the reaction vessels containing the template, on ice. The reaction vessels were then transferred to the thermal cycler. The PCR programs used are shown in Table 3, with cycling from T1→T2→T3→T1.

**Table 3      PCR thermal cycling programs**

15

	Program 1	Program 2	Program 3	Program 4
T1 (temp/duration)	96°C/30 seconds	94°C/60 seconds	94°C/90 seconds	95°C/90 seconds
T2 (temp/duration)	50°C/15 seconds	55°C/90 seconds	60°C/90 seconds	63°C/60 seconds
T3 (temp/duration)	60°C/240 seconds	72°C/60 seconds	72°C/120 seconds	72°C/60 seconds
Cycles	25	35	35	35

**List of DNA and protein accession numbers of genes used in results**

20

Gene Name	Description	cDNA Accession Number	Protein Accession Number
WNT2B	wingless-type MMTV integration site family, member 2B	AB045116	Q93097

	member 2B		
SFRP1	secreted frizzled-related protein 1	AF056087	AAC12877
SFRP4	secreted frizzled-related protein 4	AF026692	AAC04617
FRZB	frizzled-related protein	NM_001463	NP_001454
SFRP2	secreted frizzled-related protein 2		
FZD1	frizzled (Drosophila) homolog 1	AB017363	BAA34666
FZD2	frizzled (Drosophila) homolog 2	NM_001466	NP_001457
FZD9	frizzled (Drosophila) homolog 9	HSU82169	AAC51174
FZD3	frizzled (Drosophila) homolog 3	Kirikoshi et. al., 2000	Kirikoshi et. al., 2000
FZD5	frizzled (Drosophila) homolog 5		
FZD4	frizzled (Drosophila) homolog 4	NM_012193	NP_036325
FZD6	frizzled (Drosophila) homolog 6	AB012911	BAA25686
FZD7	frizzled (Drosophila) homolog 7	AB017365	BAA34668
DVL2	dishevelled 2 (homologous to Drosophila dsh)	NM_004422	NP_004413
DVL3	dishevelled 3 (homologous to Drosophila dsh)	NM_004423	NP_004414
GSK3B	glycogen synthase kinase 3 beta	NM_002093	NP_002084
AXIN1	axin	AF009674	AAC51624
APC	adenomatosis polyposis coli	NM_000038	NP_000029
TCF1	transcription factor 1, hepatic; LF-B1, hepatic nuclear factor (HNF1), albumin proximal factor	M57732	AAA88077

### Examples

Expression of a single Wnt gene, Wnt-13(2B) was detected. This transcript was absent in NTERA2 EC cells, but showed marked up-regulation following RA treatment, figure 24. Members of the FRP family, encoding putative Wnt antagonists,

also showed altered expression during differentiation, figure 24. Both Frp-1 and SARP-1 were down-regulated following RA treatment, whilst FrpHE was absent in EC cells, but expressed at high levels in RA treated cultures.

- 5 Several members of the frizzled family were also detected, providing a candidate receptor system for Wnt-13, figure 24. Two of these, hFz-4 and hFz-6, showed developmental regulation. Transcripts corresponding to intracellular components of the Wnt pathway, including Dishevelled, GSK-3b, Axin, APC and TCF were present at equivalent levels in EC and differentiating cultures. CBP was also ubiquitously  
10 expressed.

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CLAIMS

1. A method to modulate the differentiation of an embryonic stem cell  
5 comprising:
- i) providing a culture of embryonic stem cells;
  - ii) providing at least one ligand, or the active binding fragment thereof, capable  
of binding its cognate receptor polypeptide expressed by said embryonic stem  
cell;
  - 10 iii) forming a culture comprising embryonic stem cells and said ligand; and
  - iv) growing said cell culture.
2. A method according to Claim 1 wherein said ligand is encoded by a nucleic  
acid molecule selected from the group consisting of:
- 15 i) a nucleic acid molecule as represented in Figure 22;
  - ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and  
which encodes a ligand capable of binding a Wnt receptor; and
  - iii) nucleic acid molecules which are degenerate as a result of the genetic  
code to the sequences defined in (i) and (ii) above.
- 20
3. A method according to Claim 2 wherein said ligand is encoded by a nucleic  
acid molecule selected from the nucleic acid sequences represented in: Fig 30; Fig  
32; Fig 34; Fig 36; Fig 38; Fig 40; Fig 42; Fig 44; Fig 47; Fig 49; Fig 51; Fig 53; Fig  
55.
- 25
4. A method according to Claim 2 or 3 wherein said ligand is encoded by a  
nucleic acid molecule as represented by the nucleic acid sequence in Fig 22.
- 30

5. A method according to Claim 1 wherein said ligand is encoded by a nucleic acid molecule selected from the group consisting of:
- i) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, or 18.
  - 5 ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
  - iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.
- 10 6. A method according to Claim 5 wherein said ligand is selected from the group comprising the amino acid sequences in Figures 3, 6, 8, 9, 11, 13, 15, 17, 19, or polypeptide variants thereof.
- 15 7. A method according to any of Claims 1-6 wherein said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic acid; hexamethylene bisacetamide; bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog.
- 20 8. A method for modulating the differentiation of embryonic stem cells comprising:
- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
    - a) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, 18.
    - 25 b) a nucleic acid molecule which hybridises to the nucleic acid in (ii) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and
    - c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
  - 30 ii) forming a culture comprising the cell identified in (i) above with an embryonic stem cell; and

- iii) growing said culture under conditions suitable for the maintenance and/or differentiation of said embryonic stem cell.
9. A method for modulating the differentiation of embryonic stem cells comprising:
- i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
- a) a nucleic acid molecule as represented by the sequence in Figure 22;
- b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a ligand capable of binding a Wnt receptor; and
- c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- ii) forming a culture comprising a cell identified in (i) above with an embryonic stem cell; and
- iii) growing said culture under conditions suitable for the maintenance and/or differentiation of embryonic stem cells.
10. A method according to Claim 9 wherein said cell expresses Wnt-13 ligand.
11. A method according to any of Claims 9 or 10 wherein said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic acid; hexamethylene bisacetamide; bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog.
12. A method according to any of Claims 1-11 wherein said nucleic acid molecule encodes a ligand of human origin.
13. A method according to any of Claims 1-12 wherein said embryonic stem cells are of human origin.
14. A method according to any of Claims 8-13 wherein said transfected cell is a



mammalian cell.

15. A cell according to Claim 14 wherein said cell is selected from the group consisting of: a chinese hamster ovary cell; murine primary fibroblast cell; human  
5 primary fibroblast cell; transformed mouse fibroblast cell-line STO.

16. A method for inhibiting the differentiation of embryonic stem cells comprising the steps of:

- 10 i) providing at least one polypeptide, or active fragment thereof, wherein said polypeptide is an inhibitor of the *Wnt* signalling pathway.
- iii) forming a culture comprising the polypeptide identified in (i) above with an embryonic stem cell; and
- iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

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17. A method according to Claim 16 wherein said inhibitor is selected from the group consisting of the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus.

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18. A method according to Claim 17 wherein said inhibitor is encoded by a nucleic acid molecule selected from the nucleic acid sequences represented by: Fig 57; Fig 59; Fig 61; Fig 63; Fig 65; Fig 67; Fig 69; Fig 71; Fig 73; Fig 75; Fig 77; Fig 79; Fig 81; Fig 83; Fig 85; Fig 87; Fig 89; Fig 91; Fig 93; Fig 95; Fig 97; Fig 99; Fig  
25 101; or Fig 103.

19. A method for inhibiting the differentiation of embryonic stem cells comprising the steps of:

- 30 i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
  - a) a nucleic acid molecule encoding a Wnt inhibitory polypeptide;

- b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a polypeptide capable of inhibiting *Wnt* signalling; and
- c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.
- 5    ii)    forming a culture of the cell identified in (i) above with an embryonic stem cell; and
- iii)    growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.
- 10    20.    A method according to Claim 19 wherein said cells express at least one Wnt inhibitory polypeptide selected from the group consisting of the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus.
- 15    21.    A method according to Claim 19 wherein said cells express at least one Wnt inhibitory polypeptide encoded by a nucleic acid molecule selected from the nucleic acid sequences represented by : Fig 57; Fig 59; Fig 61; Fig 63; Fig 65; Fig 67; Fig 69; Fig 71; Fig 73; Fig 75; Fig 77; Fig 79; Fig 81; Fig 83; Fig 85; Fig 87; Fig 89; Fig 91; Fig 93; Fig 95; Fig 97; Fig 99; Fig 101; Fig or 103.
- 20    22.    A cell or cell culture obtainable by the method according to any of Claims 1-21.
23.    A therapeutic cell composition obtainable by the method according to any of
- 25    Claims 1-15.
24.    Use of a cell according to Claim 23 for the manufacture of a composition for use in the treatment of a disease selected from the group consisting of: Parkinson's disease; Huntington's disease; motor neurone disease; heart disease;
- 30    diabetes; liver disease (eg cirrhosis); renal disease; AIDS.

25. A method of treatment of an animal, preferably a human, comprising administering a cell composition comprising embryonic stem cells which have been induced to differentiate into at least one cell-type by the method according to any of  
5 Claims 1-14.

26. Condition medium obtained by culturing embryonic stem cells according to the method of any of Claims 1-21.

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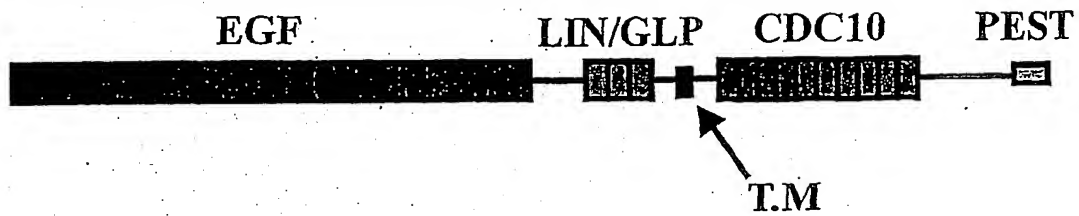
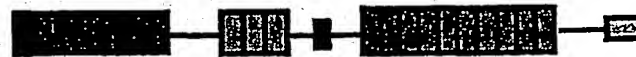
**D.melanogaster****Notch****C.elegans****Lin-12****Glp-1****Vertebrate****Notch 1, 2****Notch 3****Notch 4**

Figure 1

Figure 2

GTCCAGCGGTACCATGGGCCGTGCGAGCGCGCTAGCCCTTGCCGTGGTCTCTGCCCTGC  
TGTGCCAGGTCTGGAGCTCCGGCGTATTTGAGCTGAAGCTGCAGGAGTTCGTCAACAA  
GAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCTCTGGCCCGCCTTGCGCC  
TGCAGGACCTTCTTTTCGCGTATGCCTCAAGCACTACCAGGCCAGCGTGTACCCGGAGCC  
ACCCTGCACCTACGGCAGTGCTGTACGCCAGTGCTGGGTGTGACTCCTTCAGCCTGC  
CTGATGGCGCAGGCATCGACCCCGCCTTCAGCAACCCCATCCGATTCCCCTTCGGCTTC  
ACCTGGCCAGGTACCTTCTCTCTGATCATTGAAGCCCTCCATACAGACTCTCCCGATGA  
CCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCCTGACCACACAGAGGCACCTC  
ACTGTGGGAGAAGAATGGTCTCAGGACCTTCACAGTAGCGGCCGCACAGACCTCCGGT  
ACTCTTACCGGTTTGTGTGTGACGAGCACTACTACGGAGAAGGTTGCTCTGTGTTCTGC  
CGACCTCGGGATGACGCCTTTGGCCACTTCACCTGCGGGGACAGAGGGGAGAAGATGT  
GCGACCCTGGCTGGAAAGGCCAGTACTGCACTGACCCAATCTGTCTGCCAGGGTGTGA  
TGACCAACATGGATACTGTGACAAACCAGGGGAGTGCAAGTGCAGAGTTGGCTGGCAG  
GGCCGCTACTGCGATGAGTGCATCCGATACCCAGGTTGTCTCCATGGCACCTGCCAGC  
AACCCTGGCAGTGTAAGTCCAGGAAGGCTGGGGGGGCTTTTCTGCAACCAAGACCT  
GAACTACTGTACTACCATAAGCCGTGCAGGAATGGAGCCACCTGCACCAACACGGGC  
CAGGGGAGCTACACATGTTCTGCGACCTGGGTATACAGGTGCCAACTGTGAGCTGG  
AAGTAGATGAGTGTGCTCCTAGCCCCTGCAAGAACGGAGCGAGCTGCACGGACCTTGA  
GGACAGCTTCTCTTGACCTGCCCTCCCGGCTTCTATGGCAAGGTCTGTGAGCTGAGCG  
CCATGACCTGTGCAGATGGCCCTTGCTTCAATGGAGGACGATGTTTCAAGATAACCTGAC  
GGAGGCTACACCTGCCATTGCCCTTGGGCTTCTCTGGCTTCAACTGTGAGAAGAAGAT  
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TGACTGTGCCTCCTCCCCGTGTGCAAATGGGGGCACCTGCCGGGACAGTGTGAACGAC  
TTCTCCTGTACCTGCCCACCTGGCTACACGGGGCAAGAACTGCAGCGCCCCCTGTACGAC  
GTGTGAGCATGCACCCTGCCATAATGGGGCCACCTGCCACCAGAGGGGGCCAGCGCTAC  
ATGTGTGAGTGCAGCCAGGGCTATGGCGGGCCCAACTGCCAGTTTCTGCTCCCTGAGCC  
ACCACCAGGGCCCATGGTGGTGGACCTCAGTGAGAGGCATATGGAGAGCCAGGGCGG  
GCCCTTCCCCTGGGTGGCCGTGTGTGCCGGGGTGGTGTCTTGTCTCCTGCTGCTGCTGG  
GCTGTGCTGCTGTGGTGGTCTGCGTCCGGCTGAAGCTACAGAAACACCAGCCTCCACCT  
GAACCCTGTGGGGGAGAGACAGAAACCATGAACAACCTAGCCAATTGCCAGCGCGAG  
AAGGACGTTTCTGTTAGCATCATTGGGGCTACCCAGATCAAGAACACCAACAAGAAGG  
CGGACTTTCACGGGGACCATGGAGCCAAGAAGAGCAGCTTTAAGGTCCGATACCCAC  
TGTGGACTATAACCTCGTTTCGAGACCTCAAGGGAGATGAAGCCACGGTCAGGGATACA  
CACAGCAAACGTGACACCAAGTGCCAGTCAAGAGCTCTGCAGGAGAAGAGAAGATC  
GCCCCAACACTTAGGGGTGGGGAGATTCTTGACAGAAAAAGGCCAGAGTCTGTCTACT  
CTACTTCAAAGGACACCAAGTACCAGTCGGTGTATGTTCTGTCTGCAGAAAAGGATGA  
GTGTGTTATAGCGACTGAGGTGTAAGATGGAAGCGATGTGGCAAAATTCCCATTTCTCT  
CAAATAAAATTCCAAGGATATAGCCCCGATGAATGCTGCTGAGAGAGGAAGGGAGAG  
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AGCAGAGGCGCCCGACACTGCCAGCCTAGGCTTTGGCTGCCGCTGGACTGCCTGCTGG  
TTGTTCCCATTGCACTATGGACAGTTGCTTTGAAGAGTATATATTTAAATGGACGAGTG  
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ATAAATGTATTTATGGAATATTGTGCAATGTTATTTGAGTTTTTACTGTTTTGTAAAT

Figure 3

MGRRSALALAVVSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGGSGPPCACRTFFR  
VCLKHYQASVSPEPPCTYGS AVTPVLGVDSFSLPDGAGIDPAFSNPIRFPFGFTWPGTFSLIE  
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RVGWQGRYCECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCTHHKPCRNGAT  
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LSAMTCADGPCFNGGRCSDNPDGGYTCHCPLGFSGFNCEKKMDLCGSSPCSNGA KCVDL  
GNSYLCRCQAGFSGRYCEDNVDDCASSPCANGGT CRDSVNDFSCCTCPPGYTGKNCSAPVS  
RCEHAPCHNGATCHQRGQRYMCECAQGYGGPNCQFLPEPPPGPMVVDLSE RHMESQGG  
PFPWVAVCAGVVLVLLLLLGCAAVVVCVRLKLQKHQPPPEPCGGETETMNNLANCQREK  
DVSVSIIGATQIKNTNKKADFHGDHGAKKSSFKVRYPTVDYNLVRDLKGDEATVRDTHSK  
RDTKCQSQSSAGEEKIAPT LRGGEPDRKRPE SVYSTSKDTKYQSVYVLSAEKDECVIATEV

Figure 4

CGGGCAGAGGTGGAAGAGGGGGGAGCGCCTCAAAGAAGCGATCAGAATAATAAAAGG  
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GCCGGCCCGGGCGCCCCCTGAGTCTTCTGCTCGCCCTGCTCTGTGCCCTGCGAGCCAAG  
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CACCCGCGACGAGTGTGATACGTACTTCAAAGTGTGCCTCAAGGAGTATCAGTCCCGC  
GTCACTGCCGGGGGACCCTGCAGCTTCGGCTCAGGGTCTACGCCTGTCATCGGGGGTA  
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CCGAGTGACCTGTGATGACCACTACTATGGCTTTGGCTGCAATAAGTTCTGTCTGCCA  
GAGATGACTTCTTTGGACATTATGCCTGTGACCAGAACGGCAACAAAACCTTG CATGGA  
AGGCTGGATGGGTCTTGATTGCAACAAAGCTATCTGCCGACAGGGCTGCAGTCCCAAG  
CATGGGTCTTGTAACCTTCCAGGTGACTGCAGGTGCCAGTACGGTTGGCAGGGCCTGT  
ACTGCGACAAGTGCATCCCGCACCCAGGATGTGTCCACGGCACCTGCAATGAACCCTG  
GCAGTGCCCTCTGTGAGACCAACTGGGGTGGACAGCTCTGTGACAAAGATCTGAATTAC  
TGTGGGACTCATCAGCCCTGTCTCAACCGGGGAACATGTAGCAACACTGGGCCTGACA  
AATACCAGTGCTCCTGCCAGAGGGCTACTCGGGCCCCAACTGTGAAATTGCTGAGCA  
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GAGGCCAAACCTTGTGTAAATGCCAGATCCTGTAAGAATCTGATTGCCAGCTACTACTG  
TGATTGCCCTTCTGGCTGGATGGGTGAGAACTGTGACATAAATATCAATGACTGCCTTG  
GCCAGTGTGAGAAATGACGCCTCCTGTCTGGGATTGTTAATGGTTATCGCTGTATCTGT  
CCACCTGGCTATGCAGGCGATCACTGTGAGAGAGACATCGATGAGTGTGCTAGCAACC

Figure 5

CTGCGGCCGCGCCGCGAGCTAGGCTGGGTTTTTTTTTTCTCCCTCCCTCCCCCTTTT  
TCCATGCAGCTGATCTAAAAGGGAATAAAAGGCTGCGCATAATCATAATAATAAAGA  
AGGGGAGCGCGAGAGAAGGAGAAAGCCGGGAGGTGGAAGAGGAGGGGGAGCGTCTC  
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GAAATCACTGACAAAATAATCGATCTTGTTAGTAAACGTGATGGAAACAGCTCGCTGA





NRASDYFCKCPEDYEGKNCSHLKDHCRTPCEVIDSCTVAMASNDTPEGVRYISSNVCGPH  
GKCKSQSGGKFTCDCNKGFTGTYPCHENINDCESNPCRNGGTCIDGVNSYKICISDGEWA  
YCETNINDCSQNPCHNGGTCDLVDNFYCDCKNGWKGTCHSRDSQCDEATCNGGTCY  
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SLNRMEYTV

Figure 7

GGAGCGGGCGCGCGGCGGCGGGGCCGCGGCGGGCGGGTTCGCGGGGGCAATGCGG  
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CGGCTGGGAGGGCGAGCTCTGCGACACCAATCCCAACGACTGCCTTCCCGATCCCTGC



PRAGGDQDPGFVVIPFQFAWPRSFTLIVEAWDWDNDTTPNEBLLIERVSHAGMINPEDRWK  
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 RRDCKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPPCEAWGECGAEPPST  
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 SGASAVEVAVSFSPARDLPDSSLIQGAHAIVAAITQRGNSSLLAVTEVKVETVVTGGSST  
 GLLVPVLCGAFSVLWLACVVLVWVTRKRRKERERSRLPREESANNQWAPLNPPIRPIER  
 PGGHKDVLYQCKNFTPPPRRADEALPGPAGHAAVREDEEDEDLGRGEEDSLEAEKFLSHK  
 FTKDPGRSPGRPAHWASGPKVDNRAVRSINEARYAGKE

Figure 9

MRSRTRGRPGRPLSLLLALLCALRAKVC GASGQFELEILSMQNVN GELQNGNCCGGVRN  
 PGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFSGSTPVIGGNTFNLKASRGNDNRNIV  
 LPFSFAWPRS YTLLEAWDSSNDTIQPDSSI EKASHSGMINPSRQWQTLKQNTGIAHF EYQIR  
 VTCDHYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPDCNKAICRQGCSPKH  
 GSCKLP GDCRCQYGWQGLYCDKCIHPGCVHGT CNEPWQCLCETNWGGQLCDKDLNYC  
 GTHQPC LNRGTCSNTGPDKYQCSCEPGYSGPNCEIAEHACLSDPCHNRGSKETSSGFEC  
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 VNARSCKNLIASYYCDCLPGWMGQNCNDININDCLGQCQNDASCRDLVNGYRCICPPGYAG  
 DHCERDIDECASNPC LNGGHCQNEINRFQCLCPTGFSGNLCQLDIDYCEPNPCQNGAQCYN  
 RASDYFCKCPEDYEGKNCSHLKDHCRITTTCEVIDSCTVAMASNDTPEGVRYISSNVCGPHG  
 KCKSQSGGKFTCD CNKGFTGTCHENINDCESNPCKNGGTCIDGVNSYKCICSDGWEGAH  
 CENNINDCSQNPCHYGGTCRDLVNDFYCDCKNGWKGTCHSRDSQCDEATCNNGGTCTY  
 DEVDTFKCMCPGGWEGTTCNIARNSSCLPNPCHNGGTCTVNGDSFTCVCKEGWEGPICTQ  
 NTNDCSPHPCYN SGTCVDGDNWYRCECAPGFAGPDCRININECQSSPCA F GATCVDEINGY  
 QCICPPGHSGAKCHEVSGRSCITMGRVILDGAKWDDDCNTCQCLNGRVACSKVWCGPRPC  
 RLHKSHNECPSGQSCIPVLD DQCFVRPCTGVGECRSSSLQPVKTKCTSDSYQDNCANITFT  
 FNKEMMSPLTTEHICSELRLNLKNVSAEYSIYIACEPSLSANNEIHVAISAEDIRDDGNP  
 VKEITDKIIDLVSKRDGNSSLIAA VA EVRVQRRPLKNRTDFLVPLSSVLTVAWVCCLVTAF  
 YWCVRKRRKPSSH THSAPEDNTTNVREQLNQIKNP IEKHGANTVPIKDYENKNSKMSKIR  
 THNSEVEEDDMDKHQQKVRFAKQPVYTLVDREEKAPSGTPTKHPNWTNKQDNRDLESAQ  
 SLNRMEYIV

Figure 10

TCGAGGCGGCGATGCGGGCACGCGGCTGGGGACGCCTGCCTCGGCGGCTGCTGCTGCT  
 TCGAGGCGGCGATGCGGGCACGCGGCTGGGGACGCCTGCCTCGGCGGCTGCTGCTGCT

GCGCTGCGGAACGTGAACGGGGAGCTGCTGAGCGGCGCCTGCTGTGACGGCGACGGC  
CGGACGACGCGCGCGGGGGGCTGCGGCCGCGACGAGTGCGACACGTACGTGCGCGTG  
TGCTTAAGGAGTACCAGGCCAAGGTGACGCCACGGGGCCCTGCAGCTACGGCTACG  
GCGCCACGCCCCTGCTGGGTGGCAACTCCTTCTACCTGCCGCCGGCGGGCGCTGCGGG  
GGACCGAGCGCGCGCGCGGTCTCGGACCGGCGGCCACCAGGACCCGGGCCTCGTCGTC  
ATTCCCTTTCAGTTCGCCTGGCCGCGTTCTTTACCCTCATCGTGAGGCCTGGGACTG  
GGACAATGACACCACTCCAGATGAGGAGCTGCTGATTGAGCGGGTGTGCGACGCTGGC  
ATGATCAACCCCGAGGACCGCTGGAAGAGCCTGCACTTCAGCGGCCACGTGGCACACC  
TGGAGCTGCAGATCCGAGTGCGCTGTGATGAGAACTACTACAGTGCCACCTGCAACAA  
GTTCTGCCGGCCCCGCAACGACTTCTTTGGCCACTATACCTGCGACCAGTACGGCAACA  
AGGCCTGCATGGATGGCTGGATGGGCAAAGAATGCAAAGAAGCCGTGTGTAAACAAG  
GATGTAATTTGCTCCACGGGGGATGCACTGTGCCTGGGGAGTGCAGGTGCAGCTACGG  
CTGGCAGGGCAAGTTCTGTGACGAGTGTGTCCCCTACCCTGGCTGCGTGCATGGCAGCT  
GTGTGGAGCCCTGGCACTGTGACTGTGAGACCAACTGGGGTGGCCTGCTCTGCGACAA  
AGACCTGAACTACTGTGGCAGCCACCACCCCTGTGTCAACGGGGGTACCTGCATCAAT  
GCTGAGCCTGACCAATACCTCTGCGCTGCCAGATGGCTACTTGGGCAAGAAGTGTG  
AGCGGGCTGAGCACGCCTGTGCCTCCAACCCGTGTGCCAATGGGGGCTCTTGCCACGA  
AGTGCCATCTGGCTTTGAATGCCACTGTCCGTCAGGATGGAGCGGACCCACCTGTGCG  
CTCGACATTGATGAGTGTGCCTCTAACCCATGTGCAGCGGGTGGTACCTGCGTGGATCA  
GGTGGACGGCTTCGAGTGCATCTGCCCGGAGCAGTGGGTGGGGGCTACTTGCCAGCTG  
GACGCCAATGAGTGTGAAGGGAAGCCGTGCCTTAATGCTTTTTCTTGCAAAAACCTGAT  
TGGCGGCTATTACTGTGATTGCCTCCCGGGCTGGAAGGGCATCAACTGCCAAATCAAC  
ATCAACGATTGTCATGGGCAGTGTGAGCATGGGGGACCTGCAAGGACCTGGTCAATG  
GGTACCAGTGTGTGTGCCCGCGGGGCTTTGGAGGTGCGCATTGCGAACTAGAGTACGA  
CAAGTGTGCCAGCAGCCCCTGCCGCGGGGTGGCATCTGCGAGGACCTGGTGGATGGC  
TTCCGCTGCCACTGCCACGGGGCCTCTCTGGGCTGCACTGTGAGGTGGACATGGATCT  
CTGTGAACCAAGCCCCTGCCTCAACGGTGTCTGCTGCTACAACCTTGAGGGTGACTACT  
ACTGCGCTGCCAGAAGACTTTGGTGGCAAGAAGTGTGCTCAGTGCCAGGGACACATG  
CCCTGGCGGGGCATGTAGAGTGATCGATGGCTGCGGGTTCGAGGCAGGGTCCAGGGCA  
CGCGGTGTGCGACCCTCTGGTATATGTGGCCCTCACGGGCACTGCGTTAGCCTGCCTGG  
GGGAACTTCTCCTGCATCTGTGACAGCGGCTTCACAGGCACCTACTGCCATGAAAAC  
ATTGACGACTGCATGGGCCAGCCCTGCCGCAACGGGGGCACGTGCATTGACGAAGTGG  
ACTCCTTCCGCTGCTTCTGCCCCAGTGGCTGGGAAGGAGAACTCTGTGACATCAATCCC  
AACGACTGCCTCCCCGACCCCTGCCACAGCCGCGGCCGCTGCTATGACCTGGTCAATG  
ACTTCTACTGTGCCTGTGACGATGGCTGGAAGGGCAAGACCTGCCACTCACGCGAGTT  
CCAGTGTGACGCCTACACCTGCAGCAACGGTGGCACATGCTATGACAGCGGCGACACC  
TTCCGCTGCGCGTGCCCTCCGGGCTGGAAGGGCAGCACCTGCACCATCGCCAAGAACA  
GCAGCTGTGTGCCAATCCCTGTGTGAATGGAGGCACCTGCGTGGGTAGCGGAGACTC  
TTTCTCCTGCATCTGCCGGGATGGCTGGGAGGGCCGCACCTGCACACATAACACCAAT  
GACTGCAACCCTCTGCCCTGCTATAACGGAGGCATCTGTGTTGATGGCGTCAACTGGTT  
CCGCTGCGAGTGTGCGCCTGGCTTTGCGGGTCTGACTGCCGTATCAACATTGATGAGT  
GCCAGTCCCTGCCCCTGTGCCTACGGAGCCACGTGTGTGGATGAGATCAACGGGTACCG  
CTGCAGCTGCCACCAGGTCGTTCTGGCCCCAGGTGCCAGGAAGTGGTCATATTCACG  
AGGCCCTGCTGGTCCCGGGGAATGTCCTTCCCGCATGGGAGTTCTTGATGGAAGACT  
GCAACAGCTGCCGCTGCCTGGATGGCCACCGGGATTGTAGCAAGGTATGGTGCGGATG  
GAAGCCTTGCCTGCTCTCTGGTCAAGCCAGCGATCCGAGTGCCCACTGCCCCCAGGG  
CAGCAATGTCAGGAGAAGGCCGTGGGTCAAGTGTGTCAGCCACCCTGTGAGAACTGGG  
GGGAGTGTACAGCGGAGGAGCCTCTGCCACCCAGCACCCCTGTGAGCCACGGAGCAG  
TCATTTGGACAACAAGTGTGCCCCGACTCACACTGCGCTTCAACCGTGATCAAGTGCCTC  
AGGGCACCAACCGTGGGCGCTATCTGCTCTGGAATCCGAGCCTTGCTGCCACGAGGGC  
GGCGGCACACGACCGCCTCCTCCTGCTGCTTTGTGATCGAGCATCTCGGGGGCCAGTG

CAGAGCACAGCCCACGCCATCGTGGCTGCTATCACTCAGAGAGGAAATAGCTCACTGC  
TGCTGGCTGTCAACGAGGTCAAGGTGGAAACAGTTGTTATGGGTGGCTCTTCCACAGGT  
CTGTTGGTGCCCGTGCTGTGCAGCGTGTTCAGTGTGCTGTGGCTCGCCTGTGTGGTTAT  
CTGCGTATGGTGGACACGAAAGCGCAGGAAAGAACGTGAGAGGAGCCGGCTACCACG  
GGATGAGAGCACCACAACCAGTGGGCCCCGCTCAATCCCATCCGCAACCCCATTTGAG  
CGGCCAGGCGGCAGCGGTCTGGGAACTGGGGGCCACAAGGACATACTCTACCAGTGC  
AAAAACTTCACACCGCCGCCCGCAGGGCAGGCGAGGCACTGCCCCGGGCCAGCTGGCC  
ATGGGGCTGGTGGGGAGGACGAGGAGGATGAAGAGCTGAGCCGTGGAGATGGGGACT  
CCCCAGAGGCAGAGAAGTTCATCTCACACAAGTTCACCAAAGACCCCAGCTGCTCCCT  
CGGAAGGCCAGCCTGCTGGGCTCCAGGGCCCAAAGTGGACAACCGCGCCGTGAGAAG  
TACCAAGGACGTGCGCCGTGCTGGCAGGGAGTAGCCAGCCACCAGGCTGGCACCCAG  
AACCCTTGCTGGCACCAACGCTGCCTGCCGGACCATAGGAGGCCAAGGCCGTGTGCATA  
GTTTCTTTATTTTGTGTAAAAAACAACCAAAACCAAAAAACAATGTTTATTTTAA  
CGTTTCTTTAACCTTGATAAATTATTCAACGGCTGTCAGGCGGAAAACAACGGAGTAT  
TCTCGGATCATTGCTATTTTTGTAAAGTTTCCGCGTCCGCACGCACTGTGGCAGGAGAG  
CAGGGCGTGTGTATGTGTGTGTGTGTGTGTGTCTCACC

Figure 11

MLCDKDLNYCGSHHPCVNGGTCINAEPDQYLCAPDGYLGKNCERAEHACASNPCANGG  
SCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCTVDQVDGFECICPEQWVGATC  
QLDANECEGKPCLNAFSCKNLIGGYCDCLPGWKGINCQITINDCHGQVSAWGHLOQPVN  
GYQCVCPRGFGVRHCELEYDKCASSPCRRGGICEDLVDGFRCHCPRGLSGLHCEVDMDL  
EPSPCFNGVRCYNLEGDYYCACPEDFGGKNCSVPRDTCPPGACRVIDGCGFEAGSRARGV  
APSGICGPHGHCVSLPGGNFSCICDSGFTGTCHENIDDCMGQPCRNGGTCIDEVDSFRFCF  
PSGWEGELCDINPNDCLPDPCHSRGRCYDLVNDIFYACDDGWKGKTCHSREFQCDAYTC  
SNGGTCYDSGDTFRACPPGWKGSTCTIAKNSSCVNPNPCVNGGTCVGS GDSFSCICRDGWE  
GRTCTHTNTDCNPLPCYNGGICVDGVHWFACECAPGF

Figure 12

GAAGGCCATGGTCTCCCCACGGATGTCCGGGCTCCTCTCCCAGACTGTGATCCTAGCGC  
TCATTTTCTCCCCAGACACGGCCCGCTGGCGTCTTCGAGCTGCAGATCCACTCTTTC  
GGGCCGGGTCCAGGCCCTGGGGCCCCGCGGTCCCCCTGCAGCGCCCGGCTCCCTGCC  
GCCTCTTCTTCAGAGTCTGCCTGAAGCCTGGGCTCTCAGAGGAGGCCGCCGAGTCCCCG  
TGCGCCCTGGGCGCGGCGCTGAGTGC GCGCGGACCGGTCTACACCGAGCAGCCCGGAG  
CGCCCGCGCCTGATCTCCCACTGCCCGACGGGCTCTTGCAAGGTGCCCTTCCGGGACG  
CCTGGCCTGGCACCTTCTCTTTTCATCATCGAAACCTGGAGAGAGGAGTTAGGAGACCA  
GATTGGAGGGCCCGCCTGGAGCCTGCTGGCGCGCGTGGCTGGCAGGCGGCGCTTGGCA  
GCCGGAGGCCCGTGGGCCCCGGGCATTACGCGCGCAGGCGCCTGGGAGCTGCGCTTCTC  
GTACCGCGCGCGCTGCGAGCCGCGCTGCCGTGCGGACCGCGTGCACGCGCCTCTGCCGT  
CCGCGCAGCGCCCCCTCGCGGTGCGGTCCGGGACTGCGCCCCCTGCGCACCGCTCGAGG  
ACGAATGTGAGGCGCCGCTGGTGTGCCGAGCAGGCTGCAGCCCTGAGCATGGCTTCTG  
TGAACAGCCCGGTGAATGCCGATGCCTAGAGGGCTGGACTGGACCCCTCTGCACGGTC  
CCTGTCTCCACCAGCAGCTGCCTCAGCCCCAGGGGCCCGTCTCTGCTACCACCGGATG  
CCTTGTCCCTGGGCTGGGCCCTGTGACGGGAACCCGTGTGCCAATGGAGGCAGCTGT  
AGTGAGACACCCAGGTCCTTTGAATGCACCTGCCCGCGTGGGTTCTACGGGCTGCGGT



GCTTGTGTGTCGGGGGTGCAGACCCTGACTCTGCCTACATCTGCCACTGCCCACCTGGT  
TTCCAAGGCTCCAACTGTGAGAAGAGGGTGGACCGGTGCAGCCTGCAGCCATGCCGCA  
ATGGCGGACTCTGCCTGGACCGGGCCACGCCCTGCGCTGCCGCTGCCGCGCCGGCTTC  
GCGGGTCCTCGCTGCGAGCACGACCTGGACGACTGCGCGGGCCGCGCCTGCGCTAACG  
GCGGCACGTGTGTGGAGGGCGGCGCGCACCGCTGCTCCTGCCGCTGGGCTTCGGC  
GGCCGCGACTGCCGCGAGCGCGGACCCGTGCGCCGCGCGCCCTGTGCTCACGGC  
GGCCGCTGCTACGCCCCTTCTCCGGCCTCGTCTGCGCTTTCGCTCCCGGCTACATGGG  
AGCGCGGTGTGAGTTCCCACTGACCCCGACGGCGCAAGCGCCTTGCCCGCGGCCCG  
CCGGGCCTCAGGCCCGGGGACCCTCAGCGCTACCTTTTGCCTCCGGCTCTGGGACTGCT  
CGTGGCCGCGGGCGTGGCCGGCGCTGCGCTCTTGCTGGTCCACGTGCGCCGCGGTGGC  
CACTCCCAGGATGCTGGGTCTCGCTTGCTGGCTGGGACCCCGAGCCGTCAGTCCACG  
CACTCCCGGATGCACTCAACAACCTAAGGACGAGGAGGGTCCGGGGATGGTCCGG  
CTCGTCCGTAGATTGGAATCGCCCTGAAGATGTAGACCCTCAAGGGATTTATGTCATAT  
CTGCTCCTTCCATCTACGCTCGGGAGGTAGCGACGCCCTTTTCCCCCGCTACACACT  
GGGCGCGCTGGGCAGAGGCAGCACCTGCTTTTCCCTACCCTTCTCGATTCTGTCCGT  
GAAATGAATTGGGTAGAGTCTCTGGAAGGTTTAAAGCCCATTTTCAGTTCTAACTACT  
TTCATCCTATTTTGCATCCCTCTTATCGTTTTGAGCTACCTGCCATCTTCTCTT

Figure 13

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVC  
LKPGLSEEAESPICALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPRDAWPGTFSFIE  
TWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVG  
TACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTG  
PLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGFYGLR  
CEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLC  
LDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCEVEGGGAHRCSCALGFGGRDCR  
ERADPCAARPCAHHGRCYAHFSGLVACAPGYMGARCEFPVHPDGASALPAAPPGLRPG  
DPQRYLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNN  
LRTQEGSGDGPSSSDVWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHLLF  
PYPSSILSVK

Figure 14

AAACCGGAACGGGGCCCAACTTCTGGGGCCTGGAGAAGGGAAACGAAGTCCCCCCCCG  
GTTTCCCGAGGTGCCTTTCCTCGGGCATCCTTGGTTTCGGCGGGACTTCGCAGGGCGGA  
TATAAAGAACGGCGCCTTTGGGAAGAGGCGGAGACCGGCTTTAAAGAAAGAAGTCTTG  
GTCCTGCGGCTTGGGCGAGGCAAGGGCGAGGCAGGGCGCTTTCTGCCGACGCTCCCCG  
TGGCCCTACGATCCCCCGCGCGTCCGCCGCTGTTCTAAGGAGAGAAGTGGGGGCCCCC  
CAGGCTCGCGCGTGGAGCGAAGCAGCATGGGCAGTCCGTGCGCGCTGGCCCTGGCGT  
GCTCTCGGCCTTGCTGTGTGTCAGGTCTGGAGCTCTGGGGTGTTCGAAGTGAAGCTGCAGG  
AGTTCGTCAACAAGAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCGCGG  
GGCCACCGCCGTGCGCCTGCCGACCTTCTTCCGCGTGTGCCTCAAGCACTACCAGGCCA  
GCGTGTCCCCCGAGCCGCCCTGCACCTACGGCAGCGCCGTCACCCCCGTGCTGGGCGT  
CGACTCCTTCAGTCTGCCCGACGGCGGGGGCGCCGACTCCGCGTTCAGCAACCCCATC  
CGTTCCCTTTCGGCTTACCTGGCCGGGCACCTTCTCTCTGATTATTGAAGCTCTCC  
ACACAGATTCTCCTGATGACCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCCT  
GGCCACCCAGAGGCACCTGACGGTGGGCGAGGAGTGGTCCCAGGACCTGCACAGCAG  
CGGCCGCACGGACCTCAAGTACTCTACCGCTTCGTGTGTGACGAACACTACTACGGAG  
AGGGCTGCTCCGTTTTCTGCCGTCCCCGGGACGATGCCTTCGGCCACTTCACCTGTGGG

ATCTGCCTGCCTGGATGTGATGAGCAGCATGGATTTTGTGACAAACCAGGGGAATGCA  
AGTGCAGAGTGGGCTGGCAGGGCCGGTACTGTGACGAGTGTATCCGCTATCCAGGCTG  
TCTCCATGGCACCTGCCAGCAGCCCTGGCAGTGCAACTGCCAGGAAGGCTGGGGGGGC  
CTTTTCTGCAACCAGGACCTGAACTACTGCACACACCATAAGCCCTGCAAGAATGGAG  
CCACCTGCACCAACACGGGGCCAGGGGAGCTACACTTCTCTTGCCGGCCTGGGTACACA  
GGTGCCACCTGCGAGCTGGGGATTGACGAGTGTGACCCAGCCCTTGTAAGAACGGAG  
GGAGCTGCACGGATCTCGAGAACAGCTACTCCTGTACCTGCCCCACCCGGCTTCTACGG  
CAAAATCTGTGAATTGAGTGCCATGACCTGTGCGGACGGCCCTTGCTTTAACGGGGGT  
GGTGCTCAGACAGCCCCGATGGAGGGTACAGCTGCCGCTGCCCCGTGGGCTACTCCGG  
CTTCAACTGTGAGAAGAAAATTGACTACTGCAGCTCTTACCCTGTTCTAATGGTGCCA  
AGTGTGTGGACCTCGGTGATGCCTACCTGTGCGGCTGCCAGGCCGGCTTCTCGGGGAG  
GCACTGTGACGACAACGTGGACGACTGCGCCTCCTCCCCGTGCGCCAACGGGGGCACC  
TGCCGGGATGGCGTGAACGACTTCTCCTGCACCTGCCCCGCTGGCTACACGGGCAGGA  
ACTGCAGTGCCCCCGTCAGCAGGTGCGAGCACGCACCCTGCCACAATGGGGCCACCTG  
CCACCAGAGGGGGCACGGCTATGTGTGCGAATGTGCCCGAAGCTACGGGGGTCCCAACT  
GCCAGTTCCTGCTCCCCGAGCTGCCCCCGGGCCCCAGCGGTGGTGGACCTCACTGAGAA  
GCTAGAGGGGCCAGGGCGGGCCATTCCCCTGGGTGGCGTGTGCGCCGGGGTTCATCCTTG  
TCCTCATGCTGCTGCTGGGCTGTGCCGCTGTGGTGGTCTGCGTCCGGCTGAGGCTGCAG  
AAGCACCGGCCCCCAGCCGACCCCTGCCGGGGGGGAGACGGAGACCATGAACAACCTG  
GCAACTGCCAGCGTGAGAAGGACATCTCAGTCAGCATCATCGGGGGCCACGCAGATCAA  
GAACACCAACAAAAGGCGGACTTCCACGGGGACCACAGCGCCGACAAGAATGGCTTC  
AAGGCCCCGCTACCCAGCGGTGGACATAACCTCGTGCAGGACCTCAAGGGTGACGACAC  
CGCCGTCAGGGACGCGCACAGCAAGCGTGACACCAGTGCCAGCCCCAGGGCTCCTCAG  
GGGAGGAGAAGGGGACCCCGACCACACTCAGGGGTGGAGAAGCATCGAAAGAAAAA  
GGCCGGACTCGGGCTGTTCAACTTCAAAAGACACCAAGTACCAGTCCGTGTACGTCAT  
ATCCGAGGAGAAGGATGAGTGCCTCATAGCAACTGAGGTGTAAATGGAAGTGAGAT  
GGCAAGACTCCCGTTCTCTTAAATAAGTAAATTTCCAAGGATATATGCCCCAACGAA  
TGCTGCTGAAGAGGAGGGAGGCCTCGTGGACTGCTGCTGAGAAACCGAGTTCAGACCG  
AGCAGGTTCTCCTCCTGAGGTCCTCGACGCCTGCCGACAGCCTGTGCGGGCCCGGCCG  
CTGCGGCACTGCCTTCCGTGACGTGCGCGTTGCACTATGGACAGTTGCTCTTAAGAGAA  
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GTCCTTTTTGATACGAAGATGTGCTTTTTCTAGATGGAAAAGATGTGTGTTATTTTTTG  
ATTTGTAAAAATATTTTTCATGATATCTGTAAAGCTTGAGTATTTTGTGATGTTCTGTTT  
TTATAATTTAAATTTTGGTAAATATGTACAAAGGCACTTCGGGTCTATGTGACTATATT  
TTTTGTATATAAATGTATTTATGGAATATTGTGCCAATGTTATTTGAGTTTTTTACTGT  
TTTGTTAATGAAGAAATTCCTTTTTTAAATATTTTTTCCAAAATAAATTTTATGAGGAATT  
C

Figure 15

MGSRCALALAVLSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFF  
RVCLKHYQASVSPEPPCTYGS AVTPVLGVDSFSLPDGGGADSAFSNPFRFPFGFTWPGTFSLI  
IEALHTDSPDDLATENPERLISRLATQRHLTVGEEWSQDLHSSGRTDLKYSYRFVCDHEY  
GEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLPGCDEQHGFCDKPGECK  
CRVGWQGRYCDECIRYPGCLHGTCQPWQCNCQEGWGGLFCNQDLNYCTHHKPCKNGA  
TCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCTDLENSYSCTCPPGFYKICE  
LSAMTCADGPCFNGGRCS DSPDGGYSRCVPVGYSGFNCEKKIDYCSSSPCSNGAKCVDLG  
DAYLCRCQAGFSGRHCDDNVDDCASSPCANGGTCTRDGVNDFSTCPPGYTGRNCSAPVSR  
CEHAPCHNGATCHQRGHGYVCECARSYGGPNCQFLPELPPGPAVVDLTEKLEGQGGPFP  
WVAVCAGVILVLMLLGCAAVVVCVRLRLQKHRPPADPCRGETETMNNLANCQREKDIS



VSII GATQIKNTNKKADFGDHSADKNGFKARYPAVDYNLVQDLKGDDTAVRDAHSKRD  
TKCQPQGSSGEEKGTPPTLRGGEASERKRPDSCSTSKDTKYQSVYVISEEKDECVIATEV

Figure 16

ATGGCGGCAGCGTCCCGGAGCGCCTCTGGCTGGGCGCTACTGCTGCTGGTGGCACTTT  
GGCAGCAGCGCGCGGCGGCTCCGGCGTCTTCCAGCTGCAGCTGCAGGAGTTCATCAA  
CGAGCGCGGCGTACTGGCCAGTGGGCGGCCTTGCGAGCCCGGCTGCCGGACTTTCTTC  
CGCGTCTGCCTTAAGCACTTCCAGGCGGTCTGCTCGCCCGGACCCTGCACCTTCGGGAC  
GTCTCCACGCCGGTATTGGGCACCAACTCCTTCGCTGTCCGGGACGACAGTAGCGGCG  
GGGGGCGCAACCCTCTCCAAGTCCCTTCAATTTACCTGGCCGGGTACCTTCTCGCT  
CATCATCGAAGCTTGGCACGCGCCAGGAGACGACCTGCGGCCAGAGGCCTTGCCACCA  
GATGCACTCATCAGCAAGATCGCCATCCAGGGCTCCCTAGCTGTGGGTTCAGAACTGGT  
TATTGGATGAGCAAACCAGCACCTCACAAGGCTGCGCTACTCTTACCGGGTTCATCTGC  
AGTGACAACACTATGGAGACAAGTGTCCCGCCTGTGCAAGAAGCGCAATGACCACT  
TCGGCCACTATGTGTGCCAGCCAGATGGCAACTTGTCTGCTGCCCGGTTGGACTGGG  
GAATATTGCCAACAGCCTATCTGTCTTTCGGGCTGTGATGAACAGAATGGCTACTGCA  
GCAAGCCAGCAGAGTGCCTCTGCCGCCAGGCTGGCAGGGCCGGCTGTGTAAACGAATG  
CATCCCCACAATGGCTGTGCCACGGCACCTGCAGCACTCCCTGGCAATGTACTTGTG  
ATGAGGGCTGGGGAGGCCTGTTTTGTGACCAAGATCTCAACTACTGCACCCACCACTC  
CCCATGCAAGAATGGGGCAACGTGCTCCAACAGTGGGCAGCGAAGCTACACCTGCACC  
TGTCGCCCAGGCTACACTGGTGTGGACTGTGAGCTGGAGCTCAGCGAGTGTGACAGCA  
ACCCCTGTGCAATGGAGGCAGCTGTAAGGACCAGGAGGATGGCTACCACTGCCTGTG  
TCCTCCGGGCTACTATGGCCTGCATTGTGAACACAGCACCTTGAGCTGCGCCGACTCCC  
CCTGCTTCAATGGGGGCTCCTGCCGGGAGCGCAACCAGGGGGCCAATATGCTTGTGA  
ATGTCCCCCAACTTCACCGGCTCCAAGTGCAGAGAAGAAAGTGGACAGGTGCACCAGC  
AACCCTGTGCCAACGGGGGACAGTGCCTGAACCAGGTCCAAGCCGCATGTGCCGCTG  
CCGTCTGGATTACGGGCACCTACTGTGAAGTCCACGTCAGCGACTGTGCCCGTAACC  
CTTGCGCCACGGTGGCACTTGCCATGACCTGGAGAATGGGCTCATGTGCACCTGCCC  
TGCCGGCTTCTCTGGCCGACGCTGTGAGGTGCGGACATCCATCGATGCCTGTGCCTCGA  
GTCCCTGCTTCAACAGGGCCACCTGCTACACCGACCTCTCCACAGACACCTTTGTGTGC  
AACTGCCCTTATGGCTTTGTGGGCAGCCGCTGCGAGTTCCCCGTGGGCTTGCCGCCAG  
CTTCCCCTGGGTGGCCGTCTCGCTGGGTGTGGGGCTGGCAGTGTGCTGGTACTGCTGG  
GCATGGTGGCAGTGGCTGTGCGGCAGCTGCGGCTTCGACGGCCGGACGACGGCAGCAG  
GGAAGCCATGAACAAGTGTGCGGACTTCCAGAAGGACAACCTGATTCCTGCCGCCAGC  
TAAAAACACAAACCAGAAAGAGCTGGAAGTGGACTGTGGCCTGGACAAGTCCA  
ACTGTGGCAACAGCAAAACCACACATTGGACTATAATCTGGCCCCAGGGCCCCTGGGG  
CGGGGGACCATGCCAGGAAGTTTCCCCACAGTGACAAGAGCTTAGGAGAGAAGGCGC  
CACTGCGGTTACACAGTGAAGGCCAGAGTGGGATATCAGCGATATGCTCCCCCAGG  
GACTCCATGTACCAGTCTGTGTGTTGATATCAGAGGAGAGGAATGAATGTGTGATTGC  
CACGGAGGTATAA

Figure 17

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCEPGCRTFFRV  
CLKHFQAVVSPGPCTFGTVSTPVLGINSFAVRDDSSGGGRNPLQLPFNFTWPGTFSLEAW  
HAPGDDLPEALPPDALISKIAIQGSLAVGQNWLLDEQSTLTRLRYSYRVICSDNYGDN  
CSRLCKKRNDHFHGYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYCSKPAECLCRP  
GWQGRLCNECIPHNGCRHGTCTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATCSN  
SGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHS  
-----

GPSRMCRCRPGFTGTCELVSDCARNPCAHHGGTCHDLENGLMCTCPAGFSGRRCVVRTS  
IDACASSPCFNRACTCYTDLSTDFVCNCPYGFVGSRCBFPVGLPPSFPWVAVSLGVGLAVLL  
VLLGMVAVAVRQLRLRRPDDGSREAMNNLSDFQKDNLPAAQLKNTNQKKELEVDCGLD  
KSNCGKQQNHTLDYNLAPGPLGRGTMPGKFPKSDKSLGEKAPLRLHSEKPECRISAICSPR  
DSMYQSVCLISEERNECVIATEV

Figure 18

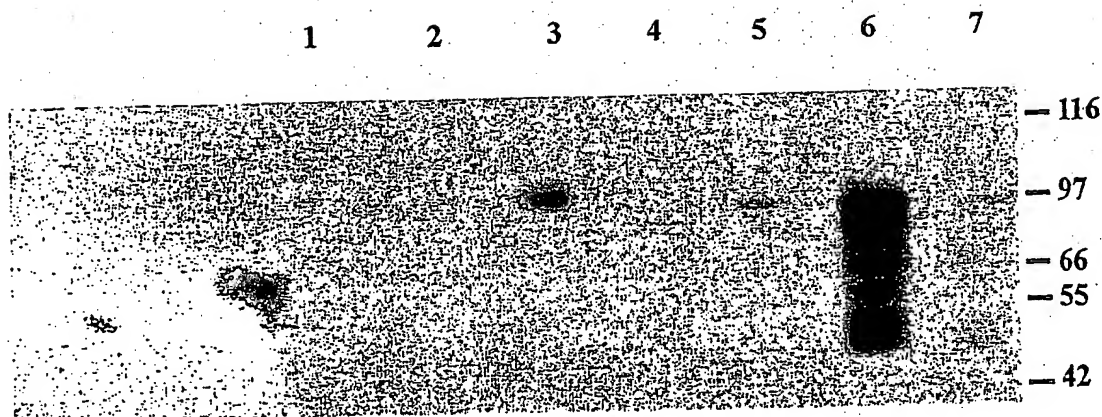
CTCGCAGGCTAGGAACCCGAGGCCAAGAGCTGCAGCCAAAGTCACTTGGGTGCAGTGT  
ACTCCCTCACTAGCCCGCTCGAGACCCTAGGATTTGCTCCAGGACACGTACTTAGAGCA  
GCCACCGCCCAGTCGCCCTCACCTGGATTACCTACCGAGGCATCGAGCAGCGGAGTTT  
TTGAGAAGGCGACAAGGGAGCAGCGTCCCAGGGGAATCAGCTTTTCAGGAACTCGGCT  
GGCAGACGGGACTTGCGGGAGAGCGACATCCCTAACAAGCAGATTTCGGAGTCCCGGA  
GTGGAGAGGACACCCCAAGGGATGACGCCTGCGTCCCAGGAGCGCCTGTGCTGGGCGT  
ACTGCTGCTGGCGGTACTGTGGCCGAGCAGCGCGCTGCGGGCTCCGGCATCTTCCAG  
CTGCGGCTGCAGGAGTTCGTCAACCAGCGCGGTATGCTGGCCAATGGGCAGTCCTGCG  
AACC GGCTGCCGGACTTTCTTCCGCATTTGCCTTAAGCACTTCCAGGCAACCTTCTCC  
GAGGGACCCTGCACCTTTGGCAATGTCTCCACGCCGGTATTGGGCACCAACTCCTTCGT  
CGTCAGGGACAAGAATAGCGGCAGTGGTCGCAACCCTCTGCAGTTGCCCTTCAATTC  
ACCTGGCCGGGAACCTTCTCACTCAACATCCAAGCTTGGCACACACCGGGAGACGACC  
TGCGGCCAGAGACTTCGCCAGGAACTCTCTCATCAGCCAAATCATCATCCAAGGCTC  
TCTTGCTGTGGGTAAGATTTGGCGAACAGACGAGCAAAATGACACCCTCACCAGACTG  
AGCTACTCTTACCGGGTCATCTGCAGTGACAACTACTATGGAGAGAGCTGTTCTCGCT  
ATGCAAGAAGCGCGATGACCACTTCGGACATTATGAGTGCCAGCCAGATGGCAGCCTG  
TCCTGCTGCCGGGCTGGACTGGGAAGTACTGTGACCAGCCTATATGTCTTTCTGGCTG  
TCATGAGCAGAATGGTTACTGCAGCAAGCCAGATGAGTGCATCTGCCGTCCAGGTGG  
CAGGGTCGCCTGTGCAATGAATGTATCCCCACAATGGCTGTCGTATGGCACCTGCA  
GCATCCCCTGGCAGTGTGCCTGCGATGAGGGATGGGGAGGTCTGTTTTGTGACCAAGA  
TCTCAACTACTGTACTCACTCTCCGTGCAAGAATGGATCAACGTGTTCCAACAGTG  
GGCCAAAGGGTTATACCTGCACCTGTCTCCAGGCTACACTGGTGAGCACTGTGAGCT  
GGGACTCAGCAAGTGTGCCAGCAACCCCTGTGCAAAATGGTGGCAGCTGTAAGGACCAG  
GAGAATAGCTACCACTGCCTGTGTCCCCAGGCTACTATGGCCAGCACTGTGAGCATA  
GTACCTTGACCTGTGCGGACTCACCTGCTTCAATGGGGGCTCTTGCCGGGAGCGCAAC  
CAGGGGTCCAGTTATGCCTGCGAATGCCCCCAACTTTACCGGCTCTAACTGTGAGAA  
GAAAGTAGACAGGTGTACCAGCAACCCGTGTGCCAATGGAGGCCAGTGCCTGAACAG  
AGGTCCAAGCCGAACCTGCCGCTGCCGGCCTGGATTACAGGCACCCACTGTGAACTG  
CACATCAGCGATTGTGCCCGAAGTCCCTGTGCCACGGGGGCACTTGCCACGATCTGG  
AGAATGGGCCTGTGTGCACCTGCCCCGCTGGCTTCTCTGGCAGGCGCTGCGAGGTGCG  
GATAACCCACGATGCCTGTGCCTCCGGACCCTGCTTCAATGGGGCCACCTGCTACACTG  
GCCTCTCCCCAAACAACTTCGTCTGCAACTGTCCTTATGGCTTTGTGGGCAGCCGCTGC  
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GCTAGTGGTACTGCTGGTGCTGCTGGTTCATGGTGGTAGTGGCTGTGCGGCAGCTGCGGC  
TTCGGAGGCCCCGATGACGAGAGCAGGGAAGCCATGAACAATCTGCAGACTTCCAGAA  
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TGACAAGAGCTTAGGAGAGAAAGTGCCACTTCGGTTACACAGTGAGAAGCCAGAGTGTC  
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GAAGAGAGGAACGAGTGTGTGATTGCCACAGAGGTATAAGGCAGAGCCTACTCAGAC  
ACCCAGCTCCGGCCCAGCAGCTGGGCCTTCTTCTGCATTGTTTACATTGCATCCTGT  
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CCTGGCTTCAGATGGGCAGCCCCGCCAAGGGAACAGAGTTGAGGAGTTAGAGGAGCAT  
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TGCTGTAGCTCCTGTGGGCATCTGTATTTCCAAAGTGCCTTTGCCCAGACTCCATCC  
TCACAGCTGGGCCCCAAATGAGAAAGCAGAGAGGAGGCTTGCAAAGGATAGGCCTCCC  
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ACAGATGGGCTTAGGGCACGCCCCCTTTTGCCAGCCAGGGGTACAGGCCTCACTGGGGA  
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CCCAGTGTGCCCGAGACCAACCTTGAAGCCGATTTTCAAAAATCAATAATATGAGGT  
TTTGT TTTGTAGTTTATTTTGAATCTAGTATTTTGATAATTTAAGAATCAGAAGCACTG  
GCCTTTCTACATTTTATAACATTATTTTGTATATAATGTGTATTATAATATGAAACAGA  
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Figure 19

MTPASRSACRWALLLLAVLWPQQRAAGSGIFQLRLQEFVNQRGMLANGQSCEPGCRTFFR  
ICLKHFQATFSEGPCTFGNVSTPVLGTFNSFVVRDKNSGSGRNPLQLPFNFTWPGTFSLNIQA  
WHTPGDDL RPETSPGNLSIQIIIQGLAVGKIWR TDEQNDTLRLSYSYRVICSDNYYGESC  
SRLCKKRDDHFGHYECQPDGSLSCLP GWTGKYCDQPICLSGCHEQNGYCSKPDECICRPG  
WQGRLCNECIPHNGCRHGTCSIPWQCACDEGWGGLFCDQDLNYCTHHSPCKNGSTCSNS  
GPKGYTCTCLPGYTGEHCELGLSKCASNPCRNNGGSCKDQENSYHCLCPPGYYGQHCEHST  
LTCADSPCFNGGSCRERNQGSSYACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSR  
TCRCRPGFTGTHCELHISDCARSPCAHGGTCHDLENGPVCTCPAGFSGRRCVRITHDACA  
SGPCFNGATCYTGLSPNNFVCNCPYGFVGSRCFPVGLPPSFPWVAVSLGVGLVLLVLLV  
MVVVA VRQLRLRRPDDESREAMNNLSDFQKDNLPAAQLKNTNQKKELEVDCGLDKSNC  
GKLQNHTLDYNLAPGLLGRGSM PGKYPHSDKSLGEKVPLRLHSEKPECRISAICSPRDSMY  
QSVCLISEERNECVIATEV

Figure 20



**Western blot analysis of Notch 2 expression in human germ cell tumour derived cell lines.**

Western blot probed with antibody specific for the intracellular portion of human NOTCH2 and visualised using chemiluminescence. Lanes from left to right 1: BeWo, 2: TERA-1, 3: 833KE, 4: 2102 Ep 2A6, 5: 2102 Ep 4D3, 6: NTERA2/D1 8 days exposure to retinoic acid, 7: NTERA2/D1 EC cells. Molecular weight markers are indicated on the right in kDa. Notch2 protein product is visualized at approx 100 kDa

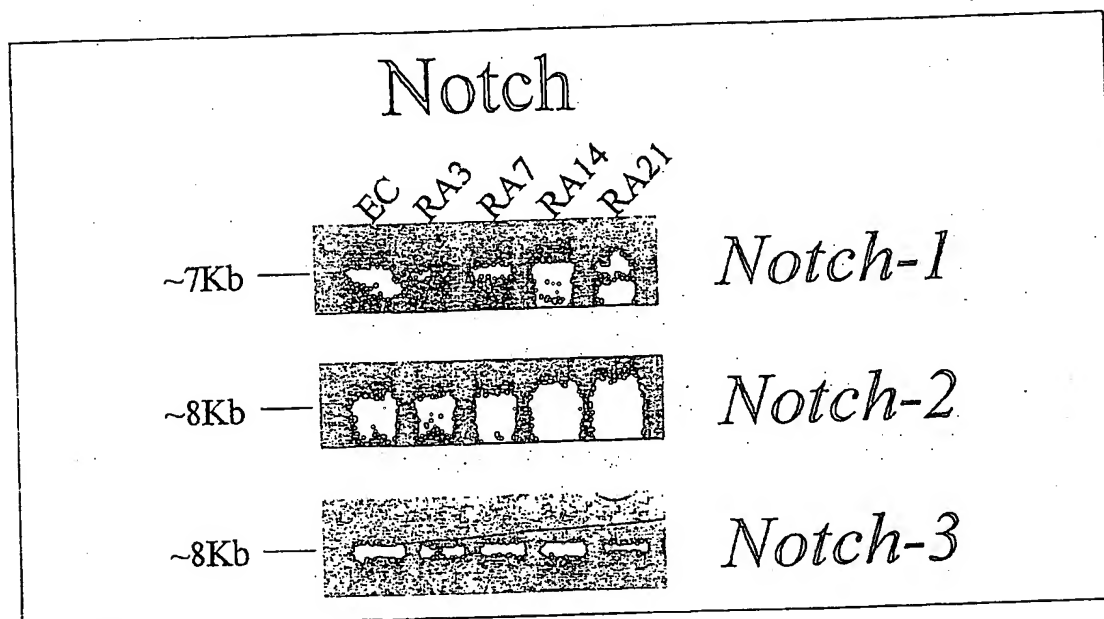
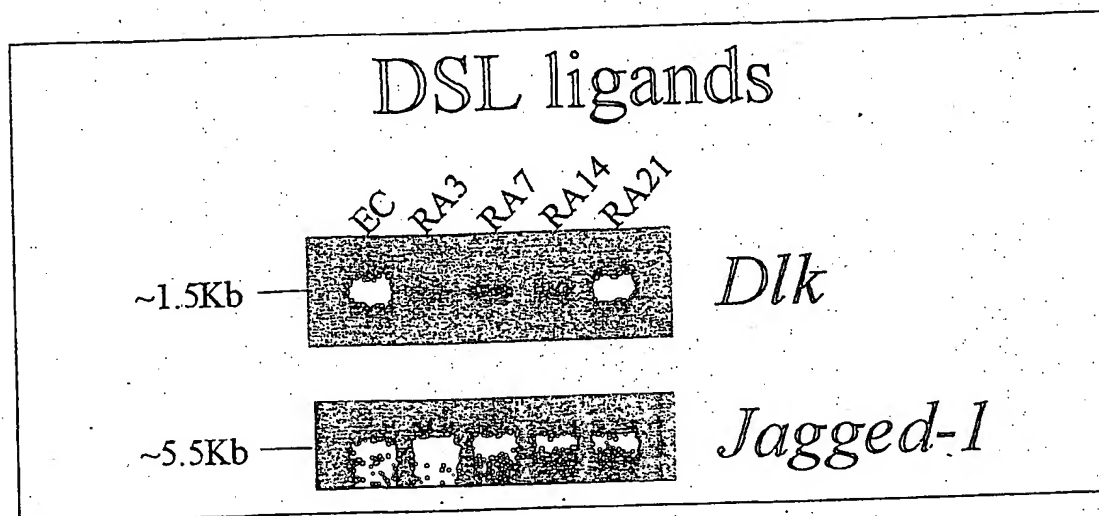
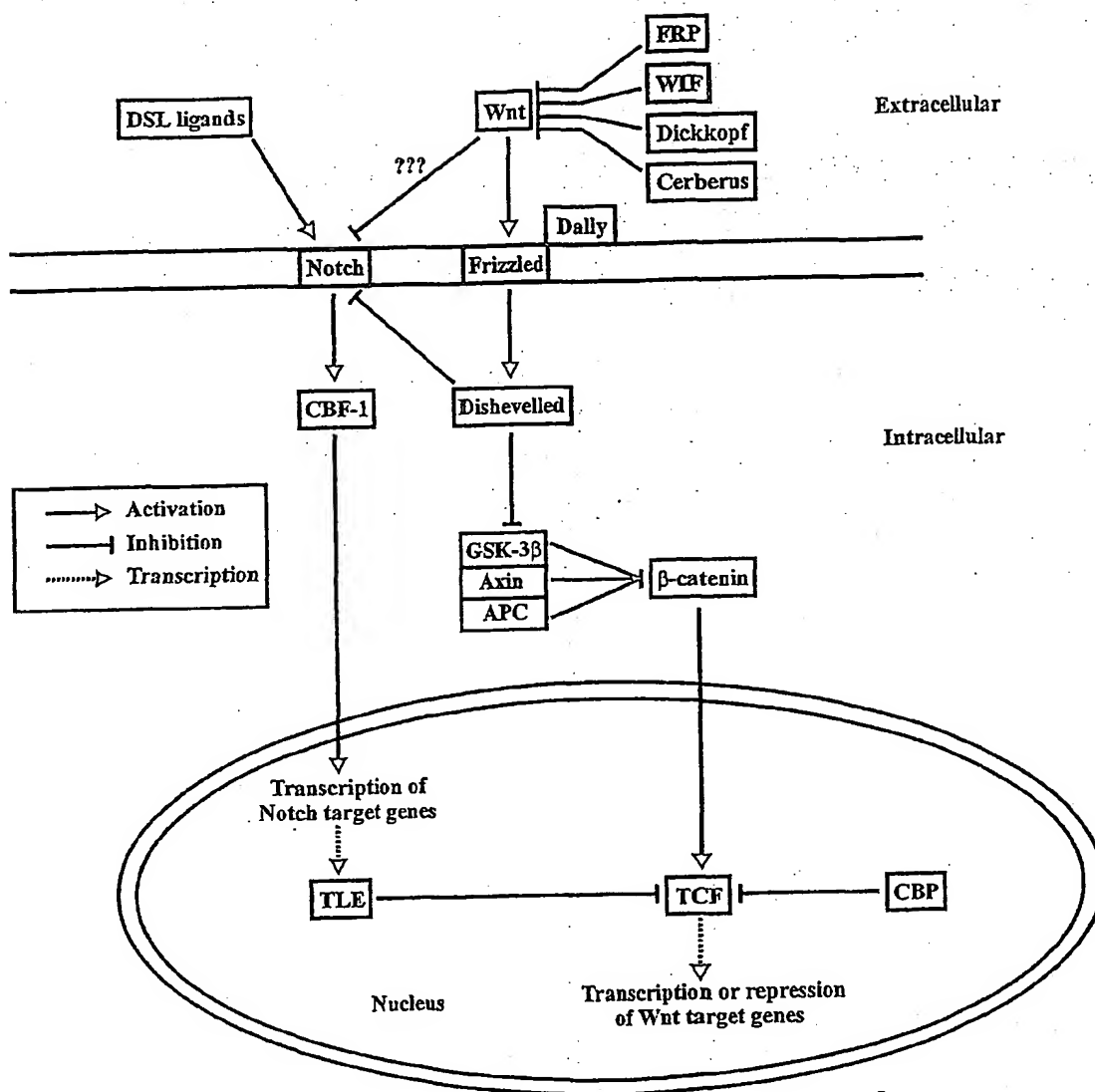


Figure 21

Figure 22

AAACCCACTCCACCTTACTACCAGACAACCTTAGCCAAACCATTACCCAAATAAAGT  
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AAAAATTATAACCAAGCATAATATAGCAAGGACTAACCCCTATACCTTCTGCATAATG  
AATTAAGTAGAAATAACTTTGCAAGGAGAGTCAAAGCTAAGGCCCGGAAACCAGGCG  
AGCTACCTAAGAACAGCTAAAAGAGCACACCCGTCTATGTAGCAAAATAGTGGGAAG  
ATTTATAGGTAGAGGCGACAAACCTACCGAGCCTGGTGATAGCTGGTTGTCCAAGATA  
GAATCTTAGTTCAACTTTAAATTTGCCCACAGAACCCCTCTAAATCCCCTTGTAATTTA  
ACTGTTAGTCCAAAGAGGAACAGCTCTTTGGACACTAGGAAAAAACCTTGTAAGAGAGA  
GTGTCAGCCCAATTCCACACTTTTCCACATGTTGGATGGCCTTGGAGTGGTAGCCATAA  
GCATTTTTTGAATTCAACTAAAACTGAAGGATCCTTGAGGACGGCAGTACCTGGCAT  
ACCTACACAGTCAGCGTTCAACAAGTGTTTGCAAAGGTACATTGGGGCACTGGGGGCA  
CGAGTGATCTGTGACAATATCCCTGGTTTGGTGAGCCGGCAGCGGCAGCTGTGCCAGC  
GTTACCCAGACATCATGCGTTCAGTGGGCGAGGGTGCCCCGAGAATGGATCCGAGAGTG  
TCAGCACCAATTCCGCCACCACCGCTGGAAGTGTACCAACCTGGACCGGGACCACACC  
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TGCAGCTGTGACCCCTACACCCGTGGCCGACACCATGACCAGCGTGGGACTTTTGAAGT  
GGGGTGGCTGCAGTGACAACATCCACTACGGTGTCGGTTTGGCAAGGCCCTTCGTGGAT  
GCCAAGGAGAAGAGGCTTAAGGATGCCCCGGGCCCTCATGAAGTACATAATAACCGCT  
GTGGTCGCACGGCTGTGCGGCGGTTTGTCAAGCTGGAGTGTAAGTGCCATGGCGTGAG  
TGGTTCCTGTACTCTGCGCACCTGCTGGCGTGCACTCTCAGATTTCCGCCGCACAGGTG  
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Fig 23



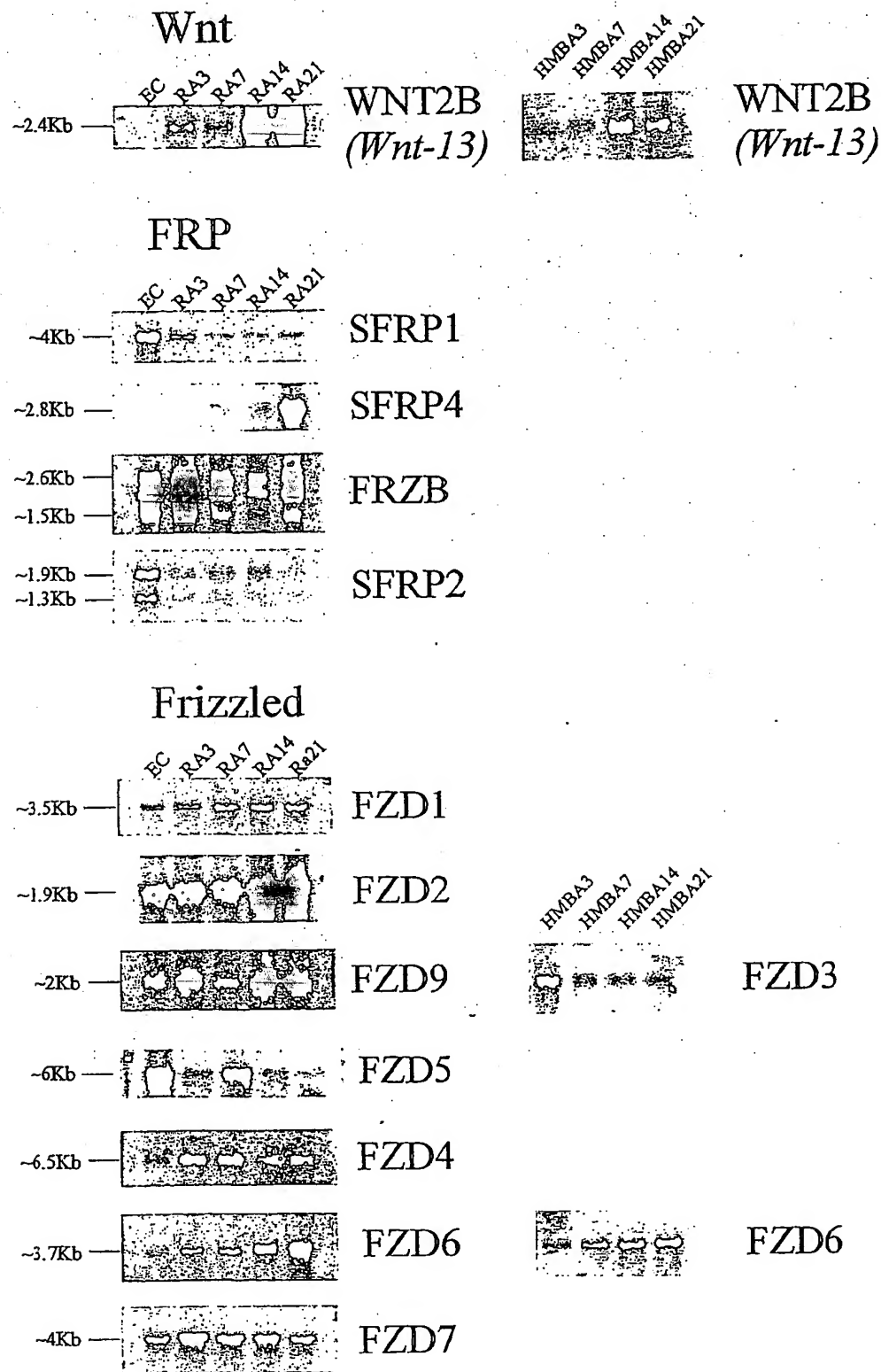


Figure 24



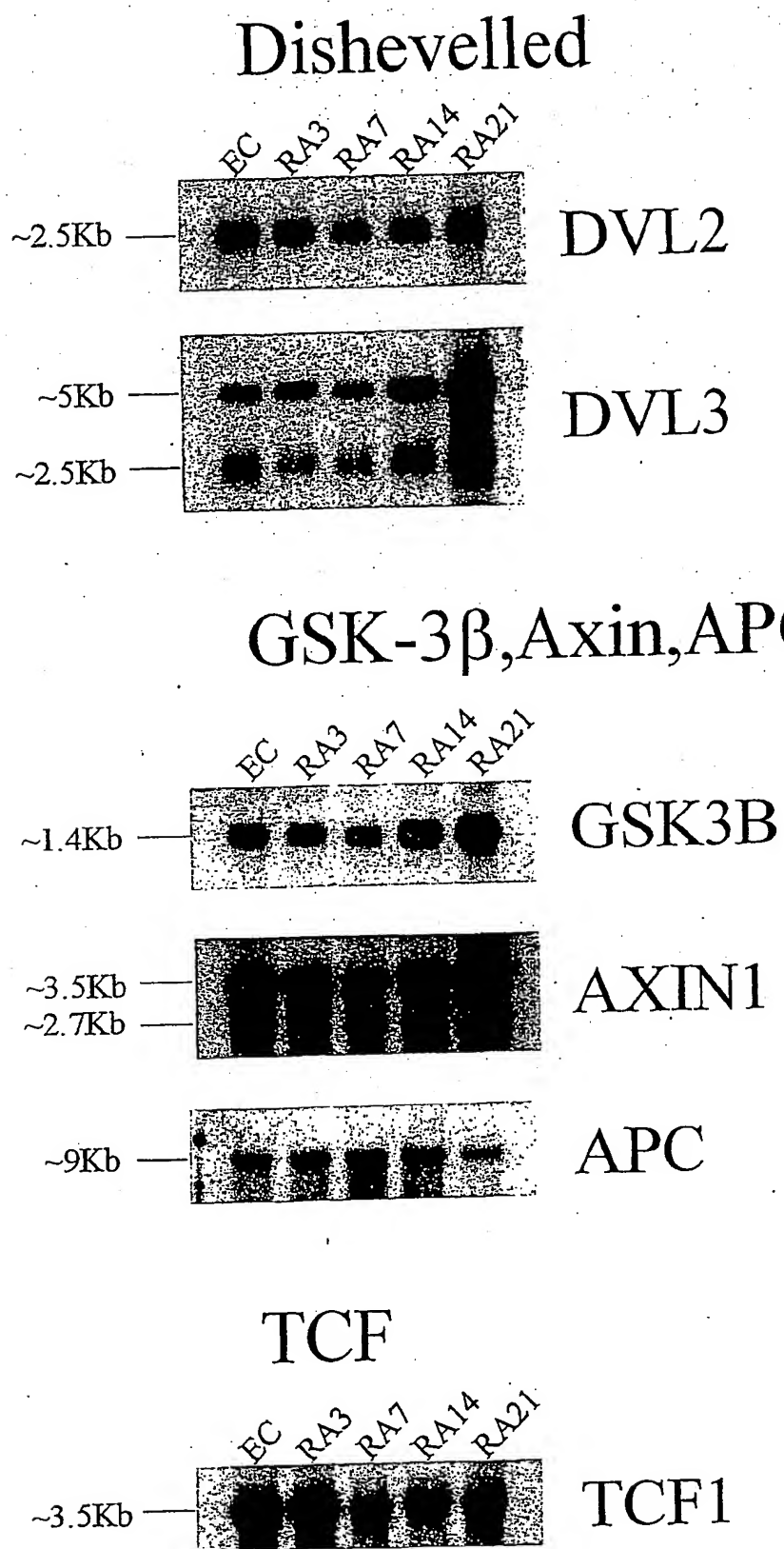


Figure 25

Figure 26

ACCGCAGGGGGCTCCCGGACCCTGACTCTGCAGCCGAACCGGCACGGTTTCGTGGGGA  
CCCAGGCTTGCAAAGTGACGGTCATTTTCTCTTTCTTTCTCCCTCTTGAGTCCTTCTGAG  
ATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTTGTGCGGATGGTAGCGGCGG  
CTCTCGGCGGCCACCCTETGCTGGGAGTGAGCGCCACCTTGAACCTCGGTTCTCAATTCC  
AACGCTATCAAGAACCTGCCCCACCGCTGGGCGGCGCTGCGGGGCACCCAGGCTCTG  
CAGTCAGCGCCGCGCCGGGAATCCTGTACCCGGGCGGGAATAAGTACCAGACCATTGA  
CAACTACCAGCCGTACCCGTGCGCAGAGGACGAGGAGTGCGGGCACTGATGAGTACTGC  
GCTAGTCCCACCCGCGGAGGGGACGCAGGCGTGCAAATCTGTCTCGCCTGCAGGAAGC  
GCCGAAAACGCTGCATGCGTCACGCTATGTGCTGCCCCGGGAATTACTGCAAAAATGG  
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TCAAAAATGTATCACACCAAAGGACAAGAAGGTTCTGTTTGTCTCCGGTCATCAGACT  
GTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCAAGATCTGTAAACCTGTCCTG  
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TTCCAGCGTTGTTACTGTGGAGAAGGTCTGTCTTGCCGGATACAGAAAGATCACCATCA  
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Figure 27

AGAAAGCGGGAGCCCGCGGCGAGCGTAGCGCAAGTCCGCTCCCTAGGCATCGCTGCGC  
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CGGGACCAAGGAGGTGCGGGGCAAGAAGGAACGGAAGCGGTGCGATCCACAGGGCTG  
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TTCCAGTTATTGCAGAACTTCCTGTCTGGTGGAGAAGCGGGTCTCGCTTGGGTTCGCG  
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Figure 28

ACACACAGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCT  
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Figure 29

GACAAACAGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGA  
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GATGGTGGCGGCCGTCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGG  
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TGTGCTGCCCTGGGACACTCTGTGTGAACGATGTTTGTACTACGATGGAAGATGCAACC  
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TCCACATTGCATTTGAG

Figure 30

ATGGGGCTCTGGGCGCTGTTGCCTGGCTGGGTTTCTGCTACGCTGCTGCTGGCGCTGGC  
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CTCGCGCGTCCTGTACGGCAACCGCGGCAGCAACCGCGCTTCGCGAGCGGAGCTGCTG  
CGCCTGGAGCCGGAAGACCCGGGCCACAAACCGCCCTCCCCCACGACCTCGTCTACT  
TCGAGAAATCGCCCAACTTCTGCACGTACAGCGGACGCCTGGGCACAGCAGGCACGGC  
AGGGCGCGCCTGTAACAGCTCGTCGCCCGCGCTGGACGGCTGCGAGCTGCTCTGCTGC  
GGCAGGGGGCCACCGCACGCGCACGCAGCGCGTACCGAGCGCTGCAACTGCACCTTCC  
ACTGGTGCTGCCACGTCAGCTGCCGCAACTGCACGCACACGCGCGTACTGCACGAGTG  
TCTGTGA

Figure 31

MGLWALLPGWVSATLLALLAALPAALAANSSGRWWGIVNVASSTNLLTDSKSLQLVLEPS  
LQLLSRKQRRRLIRQNPGLHSVSGGLQSAVRECKWQFRNRRWNCPTAPGPHLFGKIVNRGC  
RETAFFAITSAGVTHSVARSCSEGSIESCTCDYRRRGPGGPDWHWGGCSDNIDFGRLFRE  
FVDSGEKGRDLRFLMNLHNNEAGRITVFSEMROECKCHGMSGCTVRTCWMRLPTLRAV  
GDVLRDRFDGASRVLYGNRGSNRASRAELLRLEPEDPAHKPPSPHDLVYFEKSPNFCTYSG  
RLGTAGTAGRACNSSSPALDGCELLCCGRGHRTRTQRVTERCNCTFWCCHVSCRNCTHT  
RVLHECL

Figure 32

AGCAGAGCGGACGGGCGCGCGGGAGGCGCGCAGAGCTTTCGGGCTGCAGGCGCTCGC  
TGCCGCTGGGGAATTGGGCTGTGGGCGAGGCGGTCCGGGCTGGCCTTTATCGCTCGCT  
GGGCCCATCGTTTGAACTTTATCAGCGAGTCGCCACTCGTCGCAGGACCGAGCGGGG  
GGCGGGGGCGCGGCGAGGCGGCGGCCGTGACGAGGCGCTCCCGGAGCTGAGCGCTTC  
TGCTCTGGGCACGCATGGCGCCCGCACACGGAGTCTGACCTGATGCAGACGCAAGGGG  
GTAAATATGAACGCCCCCTCTCGGTGGAATCTGGCTCTGGCTCCCTCTGCTCTTGACCTG  
GCTCACCCCCGAGGTCAACTCTTCATGGTGGTACATGAGAGCTACAGGTGGCTCCTCCA  
GGGTGATGTGCGATAATGTGCCAGGCCTGGTGAGCAGCCAGCGGCAGCTGTGTACCG  
ACATCCAGATGTGATGCGTGCCATTAGCCAGGGCGTGCCGAGTGGACAGCAGAATGC  
CAGCACCAGTTCCGCCAGCACCGCTGGAATTGCAACACCCTGGACAGGGATCACAGCC  
TTTTTGGCAGGGTCTACTCCGAAGTAGTCGGGAATCTGCCTTTGTTTATGCCATCTCCT  
CAGCTGGAGTTGTATTTGCCATCACAGGGCCTGTAGCCAAGGAGAAGTAAAATCCTG  
TTCCTGTGATCCAAAGAAGATGGGAAGCGCCAAGGACAGCAAAGGCATTTTGTATTGG  
GGTGGCTGCAGTGATAACATTGACTATGGGATCAAATTTGCCCGCGCATTTGTGGATGC  
AAAGGAAAGGAAAGGAAAGGATGCCAGAGCCCTGATGAATCTTCACAACAACAGAGC  
TGGCAGGAAGGCTGTAAAGCGGTTCTTGAAACAAGAGTGCAAGTGCCACGGGGTGAG  
CGGCTCATGTACTCTCAGGACATGCTGGCTGGCCATGGCCGACTTCAGGAAAACGGGC  
GATTATCTCTGGAGGAAGTACAATGGGGCCATCCAGGTGGTCATGAACCAGGATGGCA  
CAGGTTTCACTGTGGCTAACGAGAGGTTTAAGAAGCCAACGAAAAATGACCTCGTGTA  
TTTTGAGAATTCTCCAGACTACTGTATCAGGGACCGAGAGGCAGGCTCCCTGGGTACA  
GCAGGCCGTGTGTGCAACCTGACTTCCCGGGGCATGGACAGCTGTGAAGTCATGTGCT  
GTGGGAGAGGCTACGACACCTCCCATGTACCCCGGATGACCAAGTGTGGGTGTAAGTT  
CCACTGGTGCTGCGCCGTGCGCTGTCAGGACTGCCTGGAAGCTCTGGATGTGCACACA  
TGCAAGGCCCCCAAGAACGCTGACTGGACAACCGCTACATGACCCAGCAGGCGTCAC  
CATCCACCTTCCCTTCTACAAGGACTCCATTGGATCTGCAAGAACTGGACCTTTGGG  
TTCTTTCTGGGGGGGATATTTCTTAAGGCATGTGGCCTTTATCTCAACGGAAGCCCCCTC  
TTCTTTCTGGGGGGGATATTTCTTAAGGCATGTGGCCTTTATCTCAACGGAAGCCCCCTC  
TTCTTTCTGGGGGGGATATTTCTTAAGGCATGTGGCCTTTATCTCAACGGAAGCCCCCTC

TCTATCCATCTCCTGGTGTCTGCAGTCATCTCCCCTCCTGGCGAGTTCTCTTTGGAAAT  
AGCATGACAGGCTGTTTCAGCCGGGAGGGTGGTGGGCCAGACCACTGTCTCCACCCAC  
CTTGACGTTTTCTTCTTTCTAGAGCAGTTGGCCAAGCAGAAAAAAAGTGTCTCAAAGG  
AGCTTTCTCAATGTCTTCCCACAAATGGTCCCAATTAAGAAATTCATACTTCTCTCAG  
ATGGAACAGTAAAGAAAGCAGAATCAACTGCCCTGACTTAACCTTTAACTTTTGAAAA  
GACCAAGACTTTTGTCTGTACAAGTGGTTTTACAGCTACCACCCTTAGGGTAATTGGTA  
ATTACCTGGAGAAGAATGGCTTTCAATACCCTTTTAAGTTTAAAAATGTGTATTTTTCAA  
GGCATTATTGCCATATTAATAATCTGATGTAACAAGGTGGGGACGTGTGTCTTTGGTA  
CTATGGTGTGTTGTATCTTTGTAAGAGCAAAAGCCTCAGAAAGGGATTGCTTTGCATTA  
CTGTCCCCTTGATATAAAAAATCTTTAGGGAATGAGAGTTCCTTCTCACTTAGAATCTG  
AAGGGAATTA AAAAAGAAGATGAATGGTCTGGCAATATTCTGTAACCTATTGGGTGAATA  
TGGTGGAAAATAATTTAGTGGATGGAATATCAGAAGTATATCTGTACAGATCAAGAAA  
AAAAGGAAGAATAAAATTCCTATATCAT

Figure 33

MNAPLGGIWLWLPLLLTWLTPEVNSSWWYMRATGGSSSRVMCDNVPGLVSSQRQLCHRH  
PDVMRAISQGVAEWTAECQHQRQHRWNCNTLDRDHSLFGRVLLRSSRESAFVYAISSAG  
VVFATRACSQGEVKSCSDPKKMGSAKDSKGIFDWGGCSDNIDYGIKFARAFVDAKERK  
GKDARALMNLHNNRAGRKA VKRFLKQECKCHGVSGSCTLRTCLWAMADFRKTGDYLW  
RKYNGAIQVVMNQDGTGFTVANERFKKPTKNDLVYFENSPDYCIRDREAGSLGTAGRVC  
NLTSRGMDSCEVMCCGRGYDTSHTVTRMTKCGCKFWCCAVRCQDCLEALDVHTCKAPK  
NADWTTAT

Figure 34

CGGGAGTCTTCGGGGAGCTATGCTGAGACCGGGTGGTGC GGAGGAAGCTGCGCAGCTC  
CCGCTTCGGCGCGCCAGCGCCCCGGTCCCTGTGCCGTGCGCCGCGGCCCGACGGCTC  
CCGGGCTTCGGCCCGCCTAGGTCTTGCTGCTTCTGCTCCTGCTGCTGCTGACGCTGC  
CGGCCCGCGTAGACACGTCTGGTGGTACATTGGGGCACTGGGGGCACGAGTGATCTG  
TGACAATATCCCTGGTTTGGTGAGCCGGCAGCGGCAGCTGTGCCAGCGTTACCCAGAC  
ATCATGCGTTCAGTGGGCGAGGGTGCCCGAGAATGGATCCGAGAGTGTGAGCACC  
TCCGCCACCAACCGCTGGAACGTGACCACCCTGGACCGGGACCACACCGTCTTTGGCCGT  
GTCATGCTCAGAAAGTAGCCGAGAGGCAGCTTTTGTATATGCCATCTCATCAGCAGGGG  
TAGTCCACGCTATTACTCGCGCCTGTAGCCAGGGTGAACGTGAGTGTGTGACGCTGTGAC  
CCCTACACCCGTGGCCGACACCATGACCAGCGTGGGGACTTTGACTGGGGTGGCTGCA  
GTGACAACATCCACTACGGTGTCCGTTTTGCCAAGGCCTTCGTGGATGCCAAGGAGAA  
GAGGCTTAAGGATGCCCCGGGCCCTCATGAACCTACATAATAACCGCTGTGGTTCGCACG  
GCTGTGCGGCGGTTTTCTGAAGCTGGAGTGTAAGTGCCATGGCGTGAGTGGTTCCTGTAC  
TCTGCGCACCTGCTGGCGTGCCTCTCAGATTTCCGCCGCACAGGTGATTACCTGCGGC  
GACGCTATGATGGGGCTGTGACAGGTGATGGCCACCCAAGATGGTGCCAACTTCACCGC  
AGCCCGCCAAGGCTATCGCCGTGCCACCCGGACTGATCTTGTCTACTTTGACAACTCTC  
CAGATTACTGTGTCTTGACAAAGGCTGCAGGTTCCCTAGGCACTGCAGGCCGTGTCTGC  
AGCAAGACATCAAAAGGAACAGACGGTTGTGAAATCATGTGCTGTGGCCGAGGGTAC  
GACACAACCTCGAGTCACCCGTGTTACCCAGTGTGAGTGCAAATTCCTACTGGTGTGTGC  
TGTACGGTGCAAGGAATGCAGAAATACTGTGGACGTCCATACTTGCAAAGCCCCCAAG  
AAGGCAGAGTGGCTGGACCAGACCTGAACACACAGATACCTCACTCATCCCTCCAATT  
CAAGCCTCTCAACTCAAAAGCACAAGATCCTTGATGCACACCTTCCTCCACCTCCAC  
CCTGGGCTGCTACCGCTTCTATTTAAGGATGTAGAGAGTAATCCATAGGGACCATGGTG  
TCCTGGCTGGTTCCTTAGCCCTGGGAAGGAGTTGTGAGGGGATATAAGAACTGTGCA  
AGCTCCCTGATTTCCCGCTCTGGAGATTTGAAGGGAGAGTAGAAGAGATAGGGGGTCT



ACCAGCTTCCCGACACTTCTTGGTGTGCAAGAGGAAGGGTACCTGTAGAGAGCTTCTTT  
TTGTTTCTACCTGGCCAAAGTTAGATGGGACAAAGATGAATGGCATGTCCTTCTCTGA  
AGTCCGTTTGAGCAGAACTACCTGGTACCCCGAAAGAAAAATCTTAGGCTACACATT  
CTATTATTGAGAGCCTGAGATGTTAGCCATAGTGGACAAGGTTCCATTACATGCTCAT  
ATGTTTATAAACTGTGTTTTGTAGAAGAAAAAGAATCATAACAATACAAACACACATT  
CATTCTCTCTTTTTCTCTCTACCATTCTCAACCTGTATTGGACAGCACTGCCTCTTTTGCT  
TACTTGCTGCCTGTTCAAACCTGAGGTGGAATGCAGTGGTTCCCATGCTTAACAGATCAT  
TAAACACCCCTAGAACACTCCTAGGATAGATTAATGT

Figure 35

MLDGLGVVAISIFGIQLKTEGSLRTAVPGIPTQSAFNKCLQRYIGALGARVICDNIPGLVSRQ  
RQLCQRYPDIMRSVGEAREWIRECQHQRHHRWNCTTLDRDHTVFGRVMLRSSREAAF  
VYAISSAGVIHAITRACSQGELSVCSDDPYTRGRHHDQRTGTFDWGGCSDNIHYGVRFAKAF  
VDAKEKRLKDARALMNLHNNRCGRТАVRRFVKLECKCHGVSGSCTLRTCWRALSDFRRT  
GDYLRRRYDGAVQVMATQDGANFTAARQGYRRATRSDLVYFDNSPDYCVLDKAAGSLG  
TAGRVCSKTSKGTGCEIMCCGRGYDTTRVTRVTQCECKFWCCA VRCKECRNTVDVHT  
CKAPKKAEWLDQT

Figure 36

GCGCTTCTGACAAGCCCGAAAGTCATTTCCAATCTCAAGTGGACTTTGTTCCAACATT  
GGGGGCGTCGCTCCCCCTCYTCATGGTTCGCGGGCAAACCTTCCTCCTCGGCGCCTCTTCT  
AATGGAGCCCCACCTGCTCGGGCTGCTCCTCGGCCTCCTGCTCGGTGGCACCAGGGTCC  
TCGCTGGCTACCCAATTTGGTGGTCCCTGGCCCTGGGCCAGCAGTACACATCTCTGGGC  
TCACAGCCCCCTGCTCTGCGGCTCCATCCCAGGCCTGGTCCCCAAGCAACTGCGCTTCTG  
CCGCAATTACATCGAGATCATGCCCAGCGTGGCCGAGGGCGTGAAGCTGGGCATCCAG  
GAGTGCCAGCACCAGTTCCGGGGCCCGCGCTGGAAGTGCACCACCATAGATGACAGCC  
TGGCCATCTTTGGGCCCCGTCCTCGACAAAGCCACCCGCGAGTCGGCCTTCGTTACGCGC  
ATCGCCTCGGCGGGCGTGGCCTTCGCCGTCACCCGCTCCTGCGCCGAGGGCACCTCCAC  
CATTTGCGGCTGTGACTCGCATCATAAGGGGGCCGCTGGCGAAGGCTGGAAGTGGGGC  
GGCTGCAGCGAGGACGCTGACTTCGGCGTGTTAGTGTCCAGGGAGTTTCGCGGATGCGC  
GCGAGAACAGGCCGGACGCGCGCTCGGCCATGAACAAGCACACAACGAGGCGGGCC  
GCACGACTATCCTGGACCACATGCACCTCAAATGCAAGTGCCACGGGCTGTGCGGCAG  
CTGTGAGGTGAAGACCTGCTGGTGGGCGCAGCCTGACTTCCGTGCCATCGGTGACTTCC  
TCAAGGACAAGTATGACAGCGCCTCGGAGATGGTAGTAGAGAAGCACCGTGAGTCCCG  
AGGCTGGGTGGAGACCCTCCGGGGCAAGTACTCGCTCTTCAAGCCACCCACGGAGAGG  
GACCTGGTCTACTACGAGAACTCCCCCAACTTTTGTGAGCCCAACCCAGAGACGGGTT  
CCTTTGGCACAAGGGACCGGACTTGCAATGTACCTCCACGGCATCGATGGCTGCGA  
TCTGCTCTGCTGTGGCCGGGGCCACAACACGAGGACGGAGAAGCGGAAGGAAAAATG  
CCACTGCATCTTCCACTGGTGCTGCTACGTCAGCTGCCAGGAGTGATTGCGATCTACG  
ACGTGCACACCTGCAAGTAGGGCACACG



MEPHLLGLLLGLLLGGTRVLAGYPIWWSLALGQQYTSLSGSQPLLCGSIPGLVPKQLRFCRN  
YIEIMPSVAEGVKLGIEQCQHQRFRRWNCCTTIDDSLAIFGPVLDKATRESAFVHAIASAGV  
AFAVTRSCAEGTSTICGCDSHHKGPPGEGWKWGGCSEDAFDGVLVSREFADARENRPDAR  
SAMNKHNNNEAGRRTILDHMHKCKCHGLSGSCEVKTCWWAQPFDRAIGDFLKDKYDSAS  
EMVVEKHRESRGWVETLRAKYSLFKPPTERDLVYYENSPNFCEPNPETGSFGTRDRTCNT  
SHGIDGCDLLCCGRGHNTRTEKRKEKCHCI

Figure 38

ATGAGTCCCCGCTCGTGCCTGCGTTCGCTGCGCCTCCTCGTCTTCGCCGTCTTCTCAGCC  
GCCGCGAGCAACTGGCTGTACCTGGCCAAGCTGTCGTCGGTGGGGAGCATCTCAGAGG  
AGGAGACGTGCGAGAACTCAAGGGCCTGATCCAGAGGCAGGTGCAGATGTGCAAGC  
GGAACCTGGAAGTCATGGACTCGGTGCGCCGCGGTGCCAGCTGGCCATTGAGGAGTG  
CCAGTACCAGTTCGGAACCGGCGCTGGAAGTCTCCACACTCGACTCCTTGCCCGTCT  
TCGGCAAGGTGGTGACGCAAGGGATTTCGGGAGGCGGCCTTGGTGTACGCCATCTCTTC  
GGCAGGTGTGGCCTTTGCAGTGACGCGGGCGTGCAGCAGTGGGGAGCTGGAGAAGTGC  
GGCTGTGACAGGACAGTGCATGGGGTCAGCCCACAGGGCTTCCAGTGGTCAGGATGCT  
CTGACAACATCGCCTACGGTGTGGCCTTCTCACAGTCGTTTGTGGATGTGCGGGAGAGA  
AGCAAGGGGGCCTCGTCCAGCAGAGCCCTCATGAACCTCCACAACAATGAGGCCGGCA  
GGAAGGCCATCCTGACACACATGCGGGTGGAATGCAAGTGCCACGGGGTGTGAGGCTC  
CTGTGAGGTAAAGACGTGCTGGCGAGCCGTGCCGCCCTTCCGCCAGGTGGGTACGCA  
CTGAAGGAGAAGTTTGATGGTGCCACTGAGGTGGAGCCACGCCGCGTGGGCTCCTCCA  
GGGCACTGGTGCCACGCAACGCACAGTTCAAGCCGCACACAGATGAGGACTTGGTGTA  
CTTGAGCCTAGCCCCGACTTCTGTGAGCAGGACATGCGCAGCGGCGTGCTGGGCACG  
AGGGGCCGCACATGCAACAAGACGTCCAAGGCCATCGACGGCTGTGAGCTGCTGTGCT  
GTGGCCGCGGCTTCCACACGGCGCAGGTGGAGCTGGCTGAACGCTGCAGCTGCAAATT  
CCACTGGTGCTGCTTCGTCAAGTGCCGGCAGTGCCAGCGGCTCGTGGAGTTGCACACG  
TGCCGATGA

Figure39

MSPRSLRLSLRLLVFAVFSAAASNWLYLAKLSSVGSISEEETCEKLKGLIQRQVQMCKRNL  
EVMDSVRRGAQLAIEECQYQFRNRWNCSTLDSLPVFGKVVTQGIREAALVYAISSAGVA  
FAVTRACSSGELEKCGCDRTVHGVSPQGFQWSGCSDNA YGVAFSQSFVDVRERSKGASSS  
RALMNLHNNNEAGRKAILTHMRVECKCHGVSGSCEVKTCWRAVPPFRQVGHALKEKFDG  
ATEVEPRRVGSSRALVPRNAQFKPHTDEDLVYLEPSPDFCEQDMRSGVLGTRGRTCNKTS  
KAIDGCELLCCGRGFHTAQVELAERCSCKFWCCFVKCRQCQRLVELHTCR

Figure 40.

ATTAATTCTGGCTCCACTTGTTGCTCGGCCAGGTGGGGAGAGGACGGAGGGTGGCC  
GCAGCGGGTTCCTGAGTGAATTACCCAGGAGGGACTGAGCACAGCACCAACTAGAGA  
GGGGTCAGGGGGTGCGGGACTCGAGCGAGCAGGAAGGAGGCAGCGCCTGGCACCAGG  
GCTTTGACTCAACAGAATTGAGACACGTTTGTAAATCGCTGGCGTGCCCCGCGCACAGG  
ATCCAGCGAAAATCAGATTTCTTGGTGAGGTGCGTGGGTGGATTAATTTGAAAAA  
GAAACTGCCTATATCTTGCCATCAAAAACTCACGGAGGAGAAGCGCAGTCAATCAAC  
AGTAAACTTAAGAGACCCCCGATGCTCCCCTGGTTTAACTTGTATGCTTGAAAATTATC  
TGAGAGGGAATAAACATCTTTTCTTCTTCCCTCTCCAGAAGTCCATTGGAATATTAAG  
GGGCGGAGCTTCTTGGGATGGCTGGAGTGCAATGTCTTCCAAGTTCTTCTAGTGG

CTTTGGCCATATTTTTCTCCTTCGCCCAGGTTGTAATTGAAGCCAATTCTTGGTGGTCGC  
TAGGTATGAATAACCCCTGTTTCAGATGTCAGAAGTATATATTATAGGAGCACAGCCTCTC  
TGCAGCCAACTGGCAGGACTTTCTCAAGGACAGAAGAAACTGTGCCACTTGTATCAGG  
ACCACATGCAGTACATCGGAGAAGGCGCGAAGACAGGCATCAAAGAATGCCAGTATC  
AATTCCGACATCGACGGTGGAACTGCAGCACTGTGGATAACACCTCTGTTTTTGGCAGG  
GTGATGCAGATAGGCAGCCGCGAGACGGCCTTCACATACGCCGTGAGCGCAGCAGGG  
GTGGTGAACGCCATGAGCCGGGCGTGCCGCGAGGGCGAGCTGTCCACCTGCGGCTGCA  
GCCGCGCCGCGCGCCCCAAGGACCTGCCGCGGGACTGGCTCTGGGGCGGCTGCGGCCA  
CAACATCGACTATGGCTACCGCTTTGCCAAGGAGTTCGTGGACGCCCGCGAGCGGGAG  
CGCATCCACGCCAAGGGCTCCTACGAGAGTGCTCGCATCCTCATGAACCTGCACAACA  
ACGAGGCCCGGCCGAGGACGGTGTACAACCTGGCTGATGTGGCCTGCAAGTGCCATGG  
GGTGTCCGGCTCATGTAGCCTGAAGACATGCTGGCTGCAGCTGGCAGACTTCCGCAAG  
GTGGGTGATGCCCTGAAGGAGAAGTACGACAGCGCGGGCGGCCATGCGGCTCAACAGC  
CGGGGCAAGTTGGTACAGGTCAACAGCCGCTTCAACTCGCCCACCACACAAGACCTGG  
TCTACATCGACCCCAGCCCTGACTACTGCGTGCGCAATGAGAGCACCGGCTCGCTGGG  
CACGCAGGGCCGCTGTGCAACAAGACGTCGGAGGGCATGGATGGCTGCGAGCTCATG  
TGCTGCGGCCGTGGGTACGACCAGTTCAAGACCGTGCAGACGGAGCGCTGCCACTGCA  
AGTTCCACTGGTGCTGCTACGTCAAGTGCAAGAAGTGCACGGAGATCGTGGACCAGTT  
TGTGTGCAAGTAGTGGGTGCCACCCAGCACTCAGCCCCGCTCCCAGGACCCGCTTATTT  
ATAGAAAGTACAGTGATTCTGGTTTTTGGTTTTTAGAAATATTTTTTATTTTTCCCAAG  
AATTGCAACCGGAACCATTTTTTTCTGTTACCATCTAAGAACTCTGTGGTTTATTATT  
AATATTATAATTATTATTGGCAATAATGGGGGTGGGAACCACGAAAAATATTATT  
GTGGATCTTTGAAAAGGTAATACAAGACTTCTTTTGGATAGTATAGAATGAAGGGGA  
AATAACACATACCCTAACTTAGCTGTGTGGGACATGGTACACATCCAGAAGGTAAAGA  
AATACATTTTCTTTTTCTCAAATATGCCATCATATGGGATGGGTAGGTTCCAGTTGAAA  
GAGGGTGGTAGAAATCTATTCACAATTCAGCTTCTATGACCAAAATGAGTTGTAAATTC  
TCTGGTGCAAGATAAAAGGTCTTGGGAAAACAAAACAAAACAAAACCTCCCTTC  
CCCAGCAGGGCTGCTAGCTTGCTTTCTGCATTTTCAAATGATAATTTACAATGGAAGG  
ACAAGAATGTCATATTCTCAAGGAAAAAAGGTATATCACATGTCTCATTCTCCTCAAAT  
ATTCCATTTGCAGACAGACCGTCATATTCTAATAGCTCATGAAATTTGGGCAGCAGGGA  
GGAAAGTCCCCAGAAATTAATAAAATTTAAACTCTTATGTCAAGATGTTGATTGAAAG  
CTGTTATAAGAATTGGGATTCCAGATTTGTAAAAAGACCCCCAATGATTCTGGACACTA  
GATTTTTTGTGTTGGGGAGGTTGGCTTGAACATAAATGAAATATCCTGTATTTTCTTAGG  
GATACTTGGTTAGTAAATTATAATAGTAGAAATAATACATGAATCCCATTCACAGGTTT  
CTCAGCCCAAGCAACAAGGTAATTGCGTGCCATTTCAGCACTGCACCAGAGCAGACAAC  
CTATTTGAGGAAAAACAGTGAAATCCACCTTCTCTTTCACACTGAGCCCTCTCTGATTC  
CTCCGTGTTGTGATGTGATGCTGGCCACGTTTCCAAACGGCAGCTCCACTGGGTCCCT  
TTGGTTGTAGGACAGGAAATGAAACATTAGGAGCTCTGCTTGGAAAACAGTTCACTAC  
TTAGGGATTTTTGTTTCCTAAACTTTTATTTTGGAGGAGCAGTAGTTTTCTATGTTTTAA  
TGACAGAACTTGGCTAATGGAATTCACAGAGGTGTTGCAGCGTATCACTGTTATGATCC  
TGTGTTTAGATTATCCACTCATGCTTCTCCTATTGTACTGCAGGTGTACCTTAAACTGT  
TCCCAGTGTACTTGAACAGTTGCATTTATAAGGGGGGAAATGTGGTTTAATGGTGCCTG  
ATATCTCAAAGTCTTTTGTACATAACATATATATATATATACATATATATAAATATAA  
TATAAATATATCTCATTGCAGCCAGTGATTTAGATTTACAGCTTACTCTGGGGTTATCTC  
TCTGTCTAGAGCATTGTTGTCTTCACTGCAGTCCAGTTGGGATTATCCAAAAGTTTTT  
TGAGTCTTGAGCTTGGGCTGTGGCCCCGCTGTGATCATACCTTGAGCACGACGAAGCA  
ACCTCGTTTCTGAGGAAGAAGCTTGAGTTCTGACTCACTGAAATGCGTGTTGGGTTGAA  
GATATCTTTTTTCTTTTTCTGCCTCACCCCTTTGTCTCCAACCTCCATTTCTGTTCACCTT  
GTGGAGAGGGCATTACTTGTTCTGTTATAGACATGGACGTTAAGAGATATTCAAACTC  
AGAAGCATCAGCAATGTTTCTCTTTTCTTAGTTTATTCTGCAGAATGGAAACCCATGCC  
TATTAGAAATGACAGTACTTATTAATTGAGTCCCTAAGGAATATTCAGCCCACTACATA  
GATACCTTTTTTTTTTTTTTTTTTTTTTTTATAAGGACACCTCTTTCCAAACAGGCCATCA

AATATGTTCTTATCTCAGACTTACGTTGTTTTAAAAGTTTGAAAGATACACATCTTTTC  
ATACCCCCCTTAGGAGGTTGGGCTTTCATATCACCTCAGCCAAGTGTGGCTCTTAATT  
TATTGCATAATGATATCCACATCAGCCAAGTGTGGCTCTTAATTTATTGCATAATGAT  
ATTCACATCCCCTCAGTTGCAGTGAATTGTGAGCAAAAGATCTTGAAAGCAAAAAGCA  
CTAATTAGTTTAAAATGTCACTTTTTTGGTTTTTATTATACAAAACCATGAAGTACTTT  
TTTTATTTGCTAAATCAGATTGTTCTTTTTAGTGACTCATGTTTATGAAGAGAGTTGAG  
TTTAAACAATCCTAGCTTTTAAAAGAACTATTTAATGTAAAATATTCTACATGTCATTC  
AGATATTATGTATATCTTCTAGCCTTTATTCTGTACTTTTAAATGTACATATTTCTGTCTTG  
CGTGATTGTATATTTCACTGGTTTAAAAACAAACATCGAAAGGCTTATTCCAAATGG  
AAG

Figure 41

MAGSAMSSKFFLVALAIFFSFAQVVIEANSWWSLGMNPNVQMSEVYIIGAQPLCSQLAGLS  
QGQKKLCHLYQDHMQYIGEGAKTGIKECQYQFRHRRWNCSTVDNTSVFGRVMQIGSRET  
AFTYAVSAAGVVNAMSRAAREGELSTCGCSRAARPKDLPRDWLWGGCGDNIDYGYRFA  
KEFVDARERERIHAKGSYESARILMNLHNNEAGRRTVYNLADVACKCHGVSGSCSLKTC  
WLQLADFRKVGDALKEKYDSAAAMRLNSRGKLVQVNSRFNSPTTQDLVYIDPSPDYCVR  
NESTGSLGTQGRLCNKTSEGMDCGELMCCGRGYDQFKTVQTERCHCKFWCCYVKCKK  
CTEIVDQFVCK

Figure 42

GGCACGAGCGCAGGAGACACAGGCGCTGGCTGCCCGTCCGCTCTCCGCCTCCGCCGC  
GCCCTCCTCGCCCGGGATGGGCCCCCGCCGCCCGCGGATCCCTCGCCTCCCGGCCGC  
CGCCGTTGCGCTCGCCGCGCTCGCACTGAAGCCCGGGCCCTCGCGCGCCGCGGTTTCGC  
CCCGCAGCCTCGCCCCCTGCCACCCGGGCGGCCGTAGGGCGGTACGATGCTGCCGC  
CCTTACCCTCCCGCCTCGGGCTGCTGCTGCTGCTGCTCCTGTGCCCGGCGCACGTCCGC  
GGAAGTGTGGTGGGCTGTGGGCAGCCCCCTTGGTTATGGACCCTACCAGCATCTGCAGGA  
AGGCACGGCGGCTGGCCGGGCGGCAGGCCGAGTTGTGCCAGGCTGAGCCGGAAGTGG  
TGGCAGAGCTAGCTCGGGGCGCCCGGCTCGGGGTGCGAGAGTGCCAGTTCCAGTTCCG  
CTTCCGCCGCTGGAATTGCTCCAGCCACAGCAAGGCCTTTGGACGCATCCTGCAACAG  
GACATTCCGGGAGACGGCCTTCGTGTTCCGATCACTGCGGCGGGCGCCAGCCACGCCG  
TCACGCAGGCCTGTTCTATGGGCGAGCTGCTGCAAGTGCAGGCTGCCAGGCGCCCCGCGG  
GCGGGCCCCCTCCCCGGCCCTCCGGCCTGCCCGGCACCCCGGACCCCTGGCCCCGCG  
GGCTCCCCGGAAGGCAGCGCCGCTGGGAGTGGGGAGGCTGCGGCGACGACGTGGAC  
TTCGGGGACGAGAAGTCGAGGCTCTTTATGGACGCGCGGCACAAGCGGGGACGCGGA  
GACATCCGCGCGTTGGTGCAACTGCACAACAACGAGGCGGGCAGGCTGGCCGTGCGG  
AGCCACACGCGCACCGAGTGCAAATGCCACGGGCTGTCCGGATCATGCGCGCTGCGCA  
CCTGCTGGCAGAAGCTGCCTCCATTTCCGCGAGGTGGGCGCGCGGCTGCTGGAGCGCTT  
CCACGGCGCCTCACGCGTCATGGGCACCAACGACGGCAAGGCCCTGCTGCCCGCCGTC  
CGCACGCTCAAGCCGCGGGGCGAGCGGACCTCCTACGCCGCGGATTGCCCCGACT  
TTTGCGCCCCCAACCGACGCACCGGCTCCCCCGGCACGCGCGGTGCGCGCTGCAATAG  
CAGCGCCCCGGACCTCAGCGGCTGCGACCTGCTGTGCTGCGGCCGCGGGCACCGCCAG

GAGAGCGTGCAGCTCGAAGAGAACTGCCTGTGCCGCTTCCACTGGTGCTGCGTAGTAC  
AGTGCCACCGTTGCCGTGTGCGCAAGGAGCTCAGCCTCTGCCTGTGACCCGCCGCC  
CGGCCGCTAGACTGACTTCGCGCAGCGGTGGCTCGCACCTGTGGGACCTCAGGGCACC  
GGCACCAGGGCGCCTCTCGCCGCTCGAGCCCAGCCTCTCCCTGCCAAAGCCCAACTCCC  
AGGGCTCTGGAAATGGTGAGGCGAGGGGCTTGAGAGGAACGCCCACCCACGAAGGCC  
CAGGGCGCCAGACGGCCCCGAAAAGGCGCTCGGGGAGCGTTTAAAGGACACTGTACA  
GGCCCTCCCTCCCCTTGGCCTCTAGGAGGAAACAGTTTTTTAGACTGGAAAAAAGCCA  
GTCTAAAGGCCTCTGGATACTGGGCTCCCCAGAACTGCTGGCCACAGGATGGTGGGTG  
AGGTTAGTATCAATAAAGATATTTAAACCAAAAAAAAAAAAAAAAAAAAAA

Figure 43

MLPPLPSRLGLLLLLLLCPAHVGGGLWWAVGSPLVMDPTSICRKARRLAGRQAE LCQAEPE  
VVAELARGARLGVRECQFQFRFRWNCSHSHKAFGRILQQDIRETAFVFAITAAGASHAVT  
QACSMGELLQCGCQAPRGRAPPRPSGLPGTPGPPGPAGSPEGSAAWEWGGCGDDVDFGD  
EKSRLFMDARHKRGRGDIRALVQLHNNEAGRLAVRSHRTECKCHGLSGSCALRTCWQK  
LPPFREVGARLLERFHGASRVMGTNDGKALLPAVRTLKPPGRADLLYAADSPDFCAPNRR  
TGSPGTRGRACNSSAPDLSGCDLLCCGRGHRQESVQLEENCLCRFWCCV VQCHRCVRK  
ELSLCL

Figure 44

CACGCGTCCGGGCCAATCGGGACTATGAACCGGAAAGCGCTGCGCTGCCTGGGCCACC  
TCTTTCTCAGCCTGGGCATGGTCTGCCTCCGGATCGGTGGCTTCTCCTCAGTGGTAGCTC  
TGGGCGCAACGATCATCTGTAACAAGATCCCAGGCCTGGCTCCCAGACAGCGGGCGAT  
CTGCCAGAGCCGGCCCGACGCCATCATCGTCATAGGAGAAGGCTCACAAATGGGCCTG  
GACGAGTGTCAGTTTCAGTTCGCAATGGCCGCTGGAAGTCTGCACTGGGAGAGC  
GCACCGTCTTCGGGAAGGAGCTCAAAGTGGGGAGCCGGGACGGTGCCTTACCTACGC  
CATCATTGCCGCCGGCGTGGCCACGCCATCACAGCTGCCTGTACCCATGGCAACCTG  
AGCGACTGTGGCTGCGACAAAGAGAAGCAAGGCCAGTACCACCGGGACGAGGGCTGG  
AAGTGGGGTGGCTGCTCTGCCGACATCCGCTACGGCATCGGCTTCGCCAAGGTCTTTGT  
GGATGCCCCGGGAGATCAAGCAGAATGCCCGGACTCTCATGAAGTTCACACAACGAG  
GCAGGCCGAAAGATCCTGGAGGAGAACATGAAGCTGGAATGTAAGTGCCACGGCGTG  
TCAGGCTCGTGCACCACCAAGACGTGCTGGACCACACTGCCACAGTTTCGGGAGCTGG  
GCTACGTGCTCAAGGACAAGTACAACGAGGCCGTTACAGTGAGCCTGTGCGTGCCAG  
CCGCAACAAGCGGCCACCTTCCTGAAGATCAAGAAGCCACTGTCGTACCGCAAGCCC  
ATGGACACGGACCTGGTGTACATCGAGAAGTCGCCCAACTACTGCGAGGAGGACCCGG  
TGACCGGCAGTGTGGGCACCCAGGGCCGCGCCTGCAACAAGACGGCTCCCCAGGCCAG  
CGGCTGTGACCTCATGTGCTGTGGGCGTGGCTACAACACCCACCAGTACGCCCGCGTG  
TGGCAGTGCAACTGTAAGTTCCACTGGTGTGCTATGTCAAGTGCAACACGTGCAGCG  
AGCGCACGGAGATGTACAGTGCAAGTGAGCCCCGTGTGCACACCACCTCCCGCTGC  
AAGTCAGATTGCTGGGAGGACTGGACCGTTTCCAAGCTGCGGGCTCCCTGGCAGGATG  
CTGAGCTTGTCTTTTCTGCTGAGGAAGGTAATTTCTGGGTTTCTGCAGGCATCCGTG  
GGGGAAAAAAATCTCTCAGAACCCTCAACTATTCTGTTCCACACCCAATGCTGCTCCA  
CCCTCCCCCAGACACAGCCCAAGTCCCTCCGCGGCTGGAGCGAAGCCTTCTGCAGCAG  
GAACTCTGGACCCCTGGGCCTCATCACAGCAATATTTAACAATTTATTCTGATAAAAAT  
AATATTAATTTATTTAATTAATAAAGAATTCTTCCACCTCAAAAAAAAAAAAAAAAAA  
AAAAAAAAGGGGGG

MNRKARRCLGHLFSLGMVYLRIIGGFSSVVALGASII CNKIPGLAPRQRAICQSRPDAIIVIG  
EGSQMGLDECQFQFRNGRWNC SALGERTVFGKELKVGSR EAAFTYAIIAAGVAHAIT AAC  
TQGNLSDCGCDKEKQGQYHRDEGWK WGGCSADIRY GIGFAKVFDAREIKQ NARTLMNL  
HNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEPV  
RASRNKRPTFLKIKKPLSYRKPM DTDLVYIEKSPNYCEEDPVTG SVGTQGRACNK TAPQAS  
GCDLMCCGRGYNTHQYARVWQC NCKFWCCYVKCNTCSERTEMYTCK

Figure 46

MHRNFRKWIFYVFLCFGVLYVKLGALSSVVALGANIICNKIPGLAPRQRAICQSRPDAIIVIG  
EGAQMGINECQYQFRFGRWNC SALGEKTVFGQELRVGSREAAFTYAITAAGVAHAVTAA  
CSQGNLSNCGCDREKQGYYNQAEGWK WGGCSADVRYGIDFSRRFVDAREIKKNARRLM  
NLHNNEAGRKVLED RMQLECKCHGVSGSCTTKTCWTTLPKFREVGHLLKEKYNAAVQVE  
VVRASRLRQPTFLRIKQLRSYQKPMETDLVYIEKSPNYCEEDAATG SVGTQGRLCNRTSPG  
ADGCDTMCCGRGYNTHQYTKVWQC NCKFWCCFVKCNTCSERTEVFTCK

Figure 47

TCCGCTTACACACCAAGGAAAGTTGGGCTTTGAAGAATTCCATCCCCATGGCCACTGG  
AGGAAGAATATTT CNCCCGTCTTGCTTACCCATCTCCCCAGTTTTTTGGAATTTTCTCTA  
GCTGTTACTCCAGAGGATTATGTTTCTTTCAAAGCCTTCTGTGTACATCTGTCTTTTCAC  
CTGTGTCCTCCA ACTCAGCCACAGCTGGTCGGTGAACAATTTCTGATGACTGGTCCAA  
AGGCTTACCTGATTTACTCCAGCAGTGTGGCAGCTGGTGCC CAGAGTGGTATTGAAGA  
ATGCAAGTATCAGTTTGCCTGGGACCGCTGGA ACTGCCCTGAGAGAGCCCTGCAGCTG  
TCCAGCCATGGTGGGCTTCGCAGTGCCAATCGGGAGACAGCATTGTGCATGCCATCA  
GTTCTGCTGGAGTCATGTACACCCTGACTAGAACTGCAGCCTTGAGATTTTGATAAC  
TGTGGCTGTGATGACTCCCGCAACGGGCAACTGGGGGGACAAGGCTGGCTGTGGGGAG  
GCTGCAGTGACAATGTGGGCTTCGGAGAGGCGATTTC CAAGCAGTTTGTGATGCCCT  
GGAAACAGGACAGGATGCACGGGCAGCCATGAACCTGCACAACAACGAGGCTGGCCG  
CAAGGCGGTGAAGGGCACCATGAAACGCACGTGTAAGTGCCATGGCGTGTCTGGCAGC  
TGCACCACGCAGACCTGTTGGCTGCAGCTGCCCAGATTCCGCGAGGTGGGCGCGCACC  
TGAAGGAGAAGTACCACGCAGCACTCAAGGTGGACCTGCTGCAGGGTGCTGGCAACA  
GCGCGGCCGCGCCGCGGCCATCGCCGACACCTTTCGCTCCATCTCTACCCGGGAGCTG  
GTGCACCTGGAGGACTCCCCGGA CTACTGCCTGGAGAAACAAAACGCTAGGGCTGTCTG  
GCACCGAAGGCCGAGAGTGCCTAAGGCGCGGGCGGGCCCTGGGTGCTGGGAACTCC  
GCAGCTGCCGCGGCTCTGCGGGGACTGCGGGCTGGCGGTGGAGGAGCGCGGGGGCG  
AGACCGTGTCCAGCTGCAACTGCAAGTCCACTGGTGCTGTGCAGTCCGCTGCGAGCA  
GTGCCGCGGAGGGTCACCAAGTACTTCTGTAGCCGCGCAGAGCGGCCGCGGGGGGGC  
GCTGCGCACA AACC CGGAGAAAACCCTAAGGGTTTCCTCTGCCCCCTCCTTTTCCCAC  
TGGTTCTTGGCTTCCTTTAGAGACCCCGGTAATTGTGGAACCTAGGGAATGGGGAACCC  
GCTCTCCAGACCTAGGGATCCTGAAAGGGAAAACTGCAATTTCTCAAAGCTTGCC  
ACTTTCCAGCCTGTTTCCCCAATTCCTCTGTGCTCTCCTAAAGCTCTGTCTGAATCCTCG  
CAGCCACACCTAGGTCTGAAA ACTCAGGCTTTGAGTTACTGATCTTCCTTGGATTAGGA  
AAACAGGTGTTCTCCTCCCTCTCCTATCAGCCCTAATCTCTGACCTAGCCTATCAAC  
GCTTACCGCCCTGCA A A A A C C T T C T C A T A C A C G C A G G A C C C A G G T T A A C T C A A A G C T T T

GCCCTTTTGCCCACTGTCTGCTACCAGGGGCTCACCTCTGCTGCACCTCTCTTCTGCAC  
AGCTCCTCCCCTGCTACTGCTGACCAAATTCACAGGAATCTTGAATGCTTTCTCCTCT  
TCTCCCTTTCTTTCCCAAAAAAACTGAGGAACTGGCCCCGGAAAAGCATGTCTTTG  
GGGTTGGTTCTAGAGGCAGAGGTTGAAGATGGAAGAGGGAGCTCTGGAGTGCTAACT  
TGAACACCAAGGGTGCTACTCATCCCTATGGTATCATATCATGAATGGACTTTACTAGT  
GGGGCAATGACTTTCCTAGACAATAACCCGAGGGACTCCAGATACATACCCCGAAGGT  
CTAGGAAATACGTTAAGGGCAGATTACAGTCATTTCTACCCCTTTAAAGGTAACCTTCTC  
CCTTCTCCTGACCTACTTCCTCCTAGCAACCAACTTTACCTCTTCTTCTCCAAAGGATCT  
TTGTTCTCTGAGCCAAGACTGAGGTAAATAAAGCCACTTTCCTCTTCAGATCCTGGTC  
TGCACCTCTAGA

Figure 48

MFLSKPSVYICLFTCVLQLSHSWSVNNFLMTGPKAYLIYSSSVAAGAQSIEECKYQFAWD  
RWNCPERALQLSSHGGLRSANREAFVHAISSAGVMYTLTRNCSLGDFDNCGDDSRNGQ  
LGGQGWLWGGCSDNVGFGEAISKQFVDALETGQDARAAMNLHNNEAGRKA VKGTMKR  
TCKCHGVSGSCTTQTCWLQLPEFREVGAHLKEYHAALKVDLLQGAGNSAAARGAIADT  
FRSISTREL VHLEDSPDYCLNKTLGLLGTGRECLRRGRALGRWELRSCRRLCGDCGLAV  
BERRAETVSSCNCKFWCCA VRCEQCRRRVTKYFCSRAERPRGGAAHKPGRKP

Figure 49

GCGGCCGCGTCGACGGAGGGGCTGCAGCTCCGTCAGCCCGGCAGAGCCACCCTGAGCT  
CGGTGAGAGCAAAGCCAGAGCCCCAGTCCTTTGCTCGCCGGCTTGCTATCTCTCTCGA  
TCACTCCCTCCCTTCTCCCTCCCTTCTCCCGCGCGCGCGCGGCTGGGGAAGCG  
GTGAAGAGGAGTGCCCCGGCCCTGGAAGAATGCGGCTCTGACAAGGGGACAGAACC  
AGCGCAGTCTCCCCACGGTTTAAGCAGCACTAGTGAAGCCAGGCAACCCAACCGTGC  
CTGTCTCGGACCCCGCACCCAAACCACTGGAGGTCCTGATCGATCTGCCCACCGGAGC  
CTCCGGGCTTCGACATGCTGGAGGAGCCCCGGCGCGGCTCCGCCCTCGGGCCTCGC  
GGTCTCCTGTTCTGCGTTGTGTCAGTCGGGCTCTAAGCAATGAGATTCTGGGCTGA  
AGTTGCCTGGCGAGCCGCGCTGACGGCCAACACCGTGTGCTTGACGCTGTCCGGCCT  
GAGCAAGCGGCAGCTAGACCTGTGCCTGCGCAACCCCGACGTGACGGCGTCCGCGCTT  
CAGGGTCTGCACATCGCGGTCCACGAGTGTGAGCACCAGCTGCGCGACCAAGCGCTGGA  
ACTGCTCCGCGCTTGAGGGCGGCGGCGCCCTGCCGACCAAGCGCCATCCTCAAGCG  
CGGTTTCCGAGAAAGTGCTTTTCTCTTCTCCATGCTGGCTGCTGGGGTCAATGCACGAG  
TAGCCACGGCCTGCAGCCTGGGCAAGCTGGTGAGCTGTGGCTGTGGCTGGAAGGGCAG  
TGGTGAGCAGGATCGGCTGAGGGCCAACTGCTGCAGCTGCAGGCACTGTCCCGAGGC  
AAGAGTTTCCCCACTCTCTGCCAGCCCTGGCCCTGGCTCAAGCCCCAGCCCTGGCCC  
CCAGGACACATGGGAATGGGGTGGCTGTAACCATGACATGGACTTTGGAGAGAAGTTC  
TCTCGGGATTCTTGATTCCAGGGAAGCTCCCCGGGACATCCAGGCACGAATGCGAA  
TCCACAACAACAGGGTGGGGCGCCAGGTGGTAACTGAAAACCTGAAGCGGAAATGCA  
AGTGTGATGGACATCAGGCAGCTGCCAGTTCAAGACATGCTGGAGGGCGGCCCCAGA  
GTTCCGGGCGAGTGGGGGCGGCGTTGAGGGAGCGGCTGGGCGGGGCCATCTTCATTGAT  
ACCCACAACCGCAATTCTGGAGCCTTCCAGCCCCGTCTGCGTCCCCGTGCGCTCTCAGG  
AGAGCTGGTCTACTTTGAGAAGTCTCCTGACTTCTGTGAGCGAGACCCCACTATGGGCT  
CCCCAGGGACAAGGGGCGGGCCTGCAACAAGACCAGCCGCTGTGGATGGCTGTGG  
CAGCCTGTGCTGTGGCCGTGGGCACAACGTGCTCCGGCAGACACGAGTTGAGCGCTGC  
CATTGCCGCTTCCACTGGTGCTGCTATGTGCTGTGTGATGAGTGCAAGGTTACAGAGTG  
GGTGAATGTGTGTAAGTGAGGGTCAGCCTTACCTTGGGGCTGGGGAAGAGGACTGTGT  
CAGAGCGCGCGCTTTTCAAGCCCTTTGCTCTGATTTCCTTCCAAGGTCACCTCTTGGTCCCT



GGAAGCTTAAAGTATCTACCTGGAAACAGCTTTAGGGGTGGTGGGGGTCAGGTGGACT  
CTGGGATGTGTAGCCTTCTCCCAACAATTGGAGGGTCTTGAGGGGAAGCTGCCACCC  
CTCTTCTGCTCCTTAGACACCTGAATGGACTAAGATGAAATGCACTGTATTGCTCCTCC  
CACTTCTCAACTCCAGAGCCCCCTTTAACCCCTGATTCATACTCCTTTTGGCTGGGGAGTC  
CCTATAGTTTCACCACTCCTCTCCCTTGAGGGATAACCCCAAGGCACTGTTTGGAGCCAT  
AAGATCTGTATCTAGAAAGAGATCACCCACTCCTATGTACTATCCCCAACTCCTTTAC  
TGCAGCCTGGGCTCCCTCTTGTGGGATAATGGGAGACAGTGGTAGAGAGGTTTTCTTG  
GGAAAGAGACAGAGTGCTGAGGGGCACTCTCCCTGAATCCTCAGAGAGTTGTCTGTC  
CAGGCCCTTAGGGAAGTTGTCTCCTTCCATTAGATGTTAATGGGGACCCTCCAAAGGA  
AGGGGTTTTCCCATGACTCTTGAGCCTCTTTTTCCTTCTTCAGCAGGAAGGGTGGGAA  
GGGATAATTTATCATACTGAGACTTGTCTTGGTTCCTGTTTGAACTAAAATAAATTA  
AGTTACTGGAAAAAAAAAAAAAAAAAAAAA

Figure 50

MLEEPRPRPPPSGLAGLLFLALCSRALSNEILGLKLPGEPLTANTVCLTSLGLSKRQLDLCL  
RNPDVITASALQGLHIAVHECQHQLRDQRWNCSALEGGGRLPHHSAILKRGFRESAFSFSM  
LAAGVMHAVATACSLGKLVSCGCGWKGSGEQDRLRAKLLQLQALSRGKSFPHSLPSPGP  
GSSPSPGPQDTWEWGGCNHDMDFGEKFSRDFLDSREAPRDIQARMRIHNRRVGRQVVTEN  
LKRKCKCHGTSGSCQFKTCWRAAPEFRAVGAALRERLGRAIFIDTHNRNSGAFQPRLRPRR  
LSGELVYFEKSPDFCERDPTMGSPGTRGRACNKTSRLLDGCGSLCCGRGHNVLRQTRVER  
CHCRFWCCYVLCDECKVTEWVNVCK

Figure 51

TAACCCGCCGCTCCGCTCTCCCCGGCTGCAGGCGGCGTGCAGGACCAGCGGCGGCCG  
TGCAGGCGGAGGACTTCGGCGCGGCTCCTCCTGGGTGTGACCCCGGGCGCGCCCGCCG  
CGCGACGATGAGGGCGCGGCCGCAAGTGGCTGGCGCTGTCCAAGACACCATCGGCC  
CAGACCGGCGTGTGCTATGGCATCAAGTGGCTGGCGCTGTCCAAGACACCATCGGCC  
TGGCACTGAACCAGACGCAACACTGCAAGCAGCTGGAGGGTCTGGTGTCTGCACAGGT  
GCAGCTGTGCCGACGCAACCTGGAGCTCATGCACACGGTGGTGCACGCCGCCCGCGAG  
GTCATGAAGGCCTGTGCGCCGGGCTTTGCCGACATGCGCTGGAAGTGTCTCCTCATTGA  
GCTCGCCCCCAACTATTTGCTTGACCTGGAGAGAGGGACCCGGGAGTCGGCCTTCGTG  
TATGCGCTGTGCGCCGCCACCATCAGCCACGCCATCGCCCGGGCCTGCACCTCCGGCG  
ACCTGCCCGGCTGCTCCTGCGGCCCGCTCCCAGGTGAGCCACCCGGGCGCGGGAACCG  
CTGGGGAAGATGTGCGGACAACCTCAGCTACGGGCTCCTCATGGGGGCCAAGTTTTCC  
GATGCTCCTATGAAGGTGAAAAAACAGGATCCCAAGCCAATAAACTGATGCGTCTAC  
ACAACAGTGAAGTGGGGAGACAGGCTCTGCGCGCCTCTCTGGAATGAAGTGTAAGTG  
CCATGGGGTGTCTGGCTCCTGCTCCATCCGCACCTGCTGGAAGGGGCTGCAGGAGCTG  
CAGGATGTGGCTGCTGACCTCAAGACCCGATACTGTGCGCCACCAAGGTAGTGCACC  
GACCCATGGGCACCCGCAAGCACCTGGTGCCCAAGGACCTGGATATCCGGCCTGTGAA  
GGAAGTGGGAAGTGTGTTATTTGACAGAGCTCACCTGACTTTTGCATGAAGAATGAGAAG  
GTGGGCTCCACGGGACACAAGACAGGCAGTGCAACAAGACTTCCAACGGAAGCGAC  
AGCTGCGACCTTATGTGCTGCGGGCGTGGCTACAACCCCTACACAGACCGCGTGGTCG  
AGCGGTGCCACTGTAAGTACCACTGGTGTGCTACGTACCTGCCGACGGTGTGAGCGT  
ACCGTGGAGCGCTATGTCTGCAAGTGAGGCCCTGCCCTCCGCCCCACGCAGGAGCGAG  
GACTTTGCTCAAGGACCCTCAGCAACTGGGGCCGGGGCCTGGAGACACTCCATGGAG  
CTCTGCTTGTGAATTCCAGATGCCAGGCATGGGAGGCGGCTTGTGCTTTGCCTTCACTT  
GGAAGCCACCAGGAACAGAAGGTCTGGCCACCCTGGAAGGAGNGCAGGACATCAAAG  
GAAAGGACAAAGATTAAAAATAACTTGGCAGCCTGAGNTCTGGAGTGCCACAGNNTG

GTGTAAGGAGCGGGGCTTGGGATCGGTGAGACTGATACAGACTTGACCTTTCAGGGCC  
ACAGAGACCAGCCTCCGGGAAGGGGTCTGCCCCGCTTCTTCAGAATGTTCTGCGGGAC  
CCCCTGGCCACCCCTGGGGTCTGAGCCTGCTGGGCCACCATGGAATCACTAGCTTCG  
GGTTGTAAATGTTTTCTTTTGTNTTGTCTTTTCTTCCTTGGGATGTTGGAAGCTACA  
GAAATATTTATAAAACATAGCTTTTTCTTTGGGGTGGCACTTCTCAATCCTCTTTATAT  
ATTTANATATATAAATATATATGTATATATATAATGATCTCTAATNTAAACTAGCTT  
TTTAAGCAGCTGTATGAAATAAATGCTGAGTGAGCCCCAGCCCGCCCTGCAGTCCC  
GGCCTCGTCAAGTGAACCTCGGCAGACCCTGGGGCTGGCAGAGGGAGCTCTCCAGTTTC  
CGGGCA

Figure 52

MRARPQVCEALLFALALQTGV CYGIKWLALSKTPSALALNQTQHCKQLEGLVSAQVQLCR  
SNLELMHTVVHAAREVMKACRRAFADMRWNCSSIELAPNYLLDLERGTRESAFVYALSA  
ATISHAIARACTSGDLP GCSCGPVPGPPGPNRWGRCADNLSYGLLMGAKFSDAPMKVK  
KTGSQANKLMRLHNSEVGRQALRASLEMKCKCHGVSGSCSIRTCWKGLQELQDVAADLK  
TRYLSATKVVRHPMGRKHLVPKDLDIRPVKDWELVYLQSSPDFCMKNEKVGSHGTQDR  
QCNKTSNGSDSCDLMCCGRGYNPYTDRVVERCHCKYHWCCYVTCRRCERTVERYVCK

Figure 53

GGCGCGGCAAGATGCTGGATGGGTCCCCGCTGGCGCGCTGGCTGGCCGCGGCCTTCGG  
GCTGACGCTGCTGCTCGCCGCGCTGCGCCCTTCGGCCGCTACTTCGGGGCTGACGGGCA  
GCGAGCCCCTGACCATCCTCCCGCTGACCCTGGAGCCAGAGGCGGGCCGCCCAGGCGCA  
CTACAAGGCCTGCGACCGGCTGAAGCTGGAGCGGAAGCAGCGGCGCATGTGCCGCCG  
GGACCCGGGCGTGGCAGAGACGCTGGTGGAGGCCGTGAGCATGAGTGCGCTCGAGTG  
CCAGTTCCAGTTCCGCTTTGAGCGCTGGAAGTGCACGCTGGAGGGCCGCTACCGGGCC  
AGCCTGCTCAAGCGAGGCTTCAAGGAGACTGCCTTCCTCTATGCCATCTCCTCGGCTGG  
CCTGACGCACGCACTGGCCAAGGCGTGACGCGGGCCGCGATGGAGCGCTGTACCTGC  
GATGAGGCACCCGACCTGGAGAACCCTGAGGCCTGGCAGTGGGGGGGCTGCGGAGAC  
AACCTTAAGTACAGCAGCAAGTTCGTCAAGGAATTCCTGGGCAGACGGTCAAGCAAGG  
ATCTGCGAGCCCGTGTGGACTTCCACAACAACCTCGTGGGTGTGAAGGTGATCAAGGC  
TGGGGTGGAGACCACCTGCAAGTGCCACGGCGTGTGAGGCTCATGCACGGTGCGGACC  
TGCTGGCGGCAGTTGGCGCCTTTCCATGAGGTGGGCAAGCATCTGAAGCACAAGTATG  
AGACGGCACTCAAGGTGGGCAGCACCAATGAAGCTGCCGGCGAGGCAGGTGCCA  
TCTCCCCACCACGGGGCCGTGCCTCGGGGGCAGGTGGCAGCGACCCGCTGCCCCGCAC  
TCCAGAGCTGGTGCACCTGGATGACTCGCCTAGCTTCTGCCTGGCTGGCCGCTTCTCCC  
CGGGCACCGCTGGCCGTAGGTGCCACCGTGAGAAGAACTGCGAGAGCATCTGCTGTGG  
CCGCGGCCATAACACACAGAGCCGGGTGGTGACAAGGCCCTGCCAGTGCCAGGTGCGT  
TGGTGCTGCTATGTGGAGTGACGGCAGTGACGCGAGGTGAGGAGGTCTACACCTGCA  
AGGGCTGAGTTCCCAGGCCCTGCCAGCCCTGCTGCACAGGGTGACGGCATTGCACACG  
GTGTGAAGGTCTACACCTGCACAGGCTGAGTTCCTGGGCTCGACCAGCCCAGCTGCG  
TGGGGTACAGGCATTGCACACAGTGTGAATGGGTCTACACCTGCATGGGCTGAGTCCC  
TGGGCTCAGACCTAGCAGCGTGGGGTAGTCCCTGGGCTCAGTCCCTAGCTGCATGGGGT  
GCAGGCATTGCACAGAGCATGAATGGGCCTACACCTGCCAAGGCTGAATCCCTGGGCC  
CAGCCAGCCCTGCTGCACATGGCACAGGCATTGCACACGGTGTGAGGAGTGTACACCT  
GCAAGGGCTGAGGCCCTGGGCCAGTCAGCCCTGCTGCTCAGAGTGACAGGCATTGCAC  
ATGGTGTGAGAAGGTCTACACCTGCAAGGGACGAGTCCCCGGGCTGGCCAACCCTGC  
TGTGCAGGGTGAGGGCCATGCATGCTAGTATGAGGGGTCTACACCTGCAAGGACTGAG  
AGGCTTTT



Figure 54

MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACDR  
LKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFKE  
TAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK  
EFLGRRSSKDLRARVDFHNNLVGVKVIKAGVETTCKCHGVSGSCTVRTCWRQLAPFHEVG  
KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCLA  
GRFSPGTAGRRCHREKNCESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEVY  
TCKG

Figure 55

AGCCTGCAAAAACACAGAGGGCAAAGCCAGAAAGATGGAAAGGCACCCACCCATGC  
AGCTCACCATTGCCTCAGGGAGACCCTCTTCACAGGGGCTTCTCAAAAGACCTCCCTA  
TGGTGGTTGGGCATTGCCTCCTTCGGGGTTCCAGAGAAGCTGGGCTGCGCCAATTTGCC  
GCTGAACAGCCGCCAGAAGGAGCTGTGCAAGAGGAAACCGTACCTGCTGCCGAGCAT  
CCGAGAGGGCGCCCGGCTGGGCATTGAGGAGTGCAGGAGCCAGTTCAGACACGAGAG  
ATGGAAGTGCATGATCACCGCCCGCCGCACTACCGCCCCGATGGGCGCCAGCCCCCTC  
TTTGGCTACGAGCTGAGCAGCGGCACCAAAGAGACAGCATTTATTTATGCTGTGATGG  
CTGCAGGCCTGGTGCATTCTGTGACCAGGTGATGCAGTGCAGGCAACATGACAGAGTG  
TTCCTGTGACACCACCTTGCAAGAACGGCGGCTCAGCAAGTGAAGGCTGGCACTGGGGG  
GGCTGCTCCGATGATGTCCAGTATGGCATGTGGTTCAGCAGAAAGTTCCTAGATTTCCTC  
CATCGGAAACACCACGGGCAAAGAAAACAAAGTACTATTAGCAATGAACCTACATAA  
CAATGAAGCTGGAAGGCAGGCTGTGCGCAAGTTGATGTCAGTAGACTGCCGCTGCCAC  
GGAGTTTCCGGCTCCTGTGCTGTGAAAACATGCTGGAAAACCATGTCTTCTTTTAAAA  
GATTGGCCATTTGTTGAAGGATAAATATGAAAACAGTATCCAGATATCAGACAAAATA  
AAGAGGAAAATGCGCAGGAGAGAAAAAGATCAGAGGAAAATACCAATCCATAAGGAT  
GATCTGCTCTATGTTAATAAGTCTCCCAACTACTGTGTAGAAGATAAGAAACTGGGAAT  
CCCAGGGACACAAGGCAGAGAATGCAACCGTACATCAGAGGGTGCAGATGGCTGCAA  
CCTCCTCTGCTGTGGCCGAGGTTACAACACCCATGTGGTCAGGCACGTGGAGAGGTGT  
GAGTGTAAGTTCATCTGGTGCTGCTATGTCCGTTGCAGGAGGTGTGAAAGCATGACTG  
ATGTCCACACTTGCAAGTAACCACTCCATCCAGCCTTGGGCAAGATGCCTCAGCAATAT  
ACAATGGCATTGCAACCAGAGAGGTGCCCATCCCTGTGCAGCGCTAGTAAAGTTGACT  
CTTGCAAGTGAATCCC

Figure 56

MDRAALLGLARLCAALWAALLVLPYGAQGNWMWLGIASFGVPEKLGCANLPLNSRQKEL  
CKRKPYLLPSIREGARLGIQECGSQFRHERWNCMITAAATTAPMGASPLFGYELSSGTKET  
AFIYAVMAAGLVHVSVTRSCSAGNMTECSCDITLQNGGSASEGWHWGGCSDDVQYGMWF  
SRKFLDFPIGNTTGKENKVLLAMNLHNEAGRQAVAKLMSVDCRCHGVSGSCAVKTCWK  
TMSSFEKIGHLLKDKYENSIQISDKTKRKMRRREKDQRKIPIHKDDLlyVNKSPNYCVEDK  
KLGIPTQGREGNRTSEGADGCNLLCCGRGYNTHVVRHVERCECKFIWCCYV  
RCRRCESMTDVHTCK

Figure 57

AGTTGAGGGATTGACACAAATGGTCAGGCGGCGGCGGCGGAGAAAGGAGGCGGAGGCG  
-----

CACTAGCGCGGCGCCGCCAGCCGGGAGCCAGCGAGCCGAGGGCCAGGAAGGCGGGAC  
ACGACCCCGGCGCGCCCTAGCCACCCGGGTTCTCCCCGCCGCCCGCGCTTCATGAATCG  
CAAGTTTCCGCGGGCGGGCGGGCTGCGGTACGCAGAACAGGAGCCGGGGGAGCGGGC  
CGAAAGCGGCTTGGGCTCGACGGAGGGCACCCGCGCAGAGGTCTCCCTGGCCGCAGG  
GGGAGCCGCCGCCGGCCGTGCCCTGGCAGCCCCAGCGGAGCGGGCGCCAAGAGAGGA  
GCCGAGAAAGTATGGCTGAGGAGGAGGCGCCTAAGAAAGTCCCGGGCCGCCGGCGGTG  
GCGCGAGCTGGGAACCTTTGTGCCGGGGCGCTCTCGGCCCGGCTGGCGGAGGAGGGCAG  
CGGGGACGCCGGTGGCCGCCGCCGCCAGTTGACCCCGGCGATTGGCGCGCCAG  
CTGCTGCTGCTGCTTTGGCTGCTGGAGGCTCCGCTGCTGCTGGGGGTCCGGGCCAGGC  
GGCGGGCCAGGGGCCAGGCCAGGGGGCCCGGGCCGGGGCAGCAACCGCCGCCGCCGCC  
TCAGCAGCAACAGAGCGGGCAGCAGTACAACGGCGAGCGGGGCATCTCCGTCCCGGA  
CCACGGCTATTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCGTACAACCAG  
ACCATCATGCCCAACCTGCTGGGCCACACGAACCAGGAGGACGCGGGCCTGGAGGTGC  
ACCAAGTTCTACCCTCTAGTGAAAGTGACAGTGTTCGCTGAGCTCAAGTTCTTCCTGTGC  
TCCATGTACGCGCCCGTGTGCACCGTGCTAGAGCAGGCGCTGCCGCCCTGCCGCTCCCT  
GTGCGAGCGCGCGCGCCAGGGCTGCGAGGCGCTCATGAACAAGTTCGGCTTCCAGTGG  
CCAGACACGCTCAAGTGTGAGAAAGTTCGCGTGCACGGCGCCGGCGAGCTGTGCGTGG  
GCCAGAACACGTCCGACAAGGGCACCCCGACGCCCTCGCTGCTTCCAGAGTTCTGGAC  
CAGCAACCCTCAGCACGGCGGGCGGAGGGCACCGTGGCGGCTTCCCGGGGGGCGCCGG  
CGCGTCGGAGCGAGGCAAGTTCTCCTGCCCGCGCGCCCTCAAGGTGCCCTCCTACCTCA  
ACTACCACTTCCTGGGGGAGAAGGACTGCGGCGCACCTTGTGAGCCGACCAAGGTGTA  
TGGGCTCATGTACTTCGGGGCCCGAGGAGCTGCGCTTCTCGCGCACCTGGATTGGCATT  
GGTCAAGTGTGCTGCGCCTCCACGCTCTTACGGTGCTTACGTACCTGGTGGACATG  
CGGCGCTTCAGCTACCCGGAGCGGCCCATCATCTTCTTGTCCGGCTGTTACACGGCCGT  
GGCCGTGGCCTACATCGCCGGCTTCCTCCTGGAAGACCGAGTGGTGTGTAATGACAAG  
TTCGCCGAGGACGGGGCACGCACTGTGGCGCAGGGCACCAAGAAGGAGGGCTGCACC  
ATCCTCTTCATGATGCTCTACTTCTTCAGCATGGCCAGCTCCATCTGGTGGGTGATCCTG  
TCGCTCACCTGGTTCTCTGGCGGCTGGCATGAAGTGGGGCCACGAGGCCATCGAAGCCA  
ACTCACAGTATTTTACCTGGCCGCCTGGGCTGTGCCGGCCATCAAGACCATCACCATC  
CTGGCGCTGGGCCAGGTGGACGGCGATGTGCTGAGCGGAGTGTGCTTCGTGGGGCTTA  
ACAACGTGGACGCGCTGCGTGGCTTCGTGCTGGCGCCCTCTTCGTGTACCTGTTTATC  
GGCACGTCTTTCTGCTGGCCGGCTTTGTGTCGCTCTTCCGCATCCGCACCATCATGAA  
GCACGATGGCACCAAGACCGAGAAGCTGGAGAAGCTCATGGTGCAGATTGGCGTCTTC  
AGCGTGCTGTACACTGTGCCAGCCACCATCGTCATCGCCTGCTACTTCTACGAGCAGGC  
CTTCCGGGACCAAGTGGGAACGCAGCTGGGTGGCCAGAGCTGCAAGAGCTACGCTATC  
CCCTGCCCTCACCTCCAGGCGGGCGGAGGCGCCCCGCCGCACCCGCCCATGAGCCCGG  
ACTTCACGGTCTTCATGATTAAGTACCTTATGACGCTGATCGTGGGCATCACGTCGGGC  
TTCTGGATCTGGTCCGGCAAGACCCTCAACTCCTGGAGGAAGTTCTACACGAGGCTCA  
CCAACAGCAAACAAGGGGAGACTACAGTCTGAGACCCGGGGCTCAGCCCATGCCAG  
GCCTCGGCCGGGGCGCAGCGATCCCCAAAGCCAGCGCCGTGGAGTTCGTGCCAATCC  
TGACATCTCGAGGTTTCTCTACTAGACAACTCTCTTTCGAGGCTCCTTTGAACAACTC  
AGCTCCTGCAAAAGCTTCCGTCCCTGAGGCAAAAGGACACGAGGGCCCGACTGCCAGA  
GGGAGGATGGACAGACCTCTTGCCCTCACACTCTGGTACCAGGACTGTTGCTTTTATG  
ATTGTAAATAGCCTGTGTAAGATTTTGTAAAGTATATTTGTATTTAAATGACGACCGAT  
CACGCGTTTTTCTTTTCAAAAGTTTTTAATTATTTAGGGCGGTTTAACCATTTGAGGCT  
TTTCTTCTTGCCCTTTTCGGAGTATTGCAAAGGAGCTAAAACCTGGTGTGCAACCGCAC  
AGCGCTCCTGGTCGTCTCGCGCGCCTCTCCCTACCACGGGTGCTCGGGACGGCTGGGC  
GCCAGCTCCGGGGCGAGTTCAGCACTGCGGGGTGCGACTAGGGCTGCGCTGCCAGGGT  
CACTTCCCGCCTCCTCCTTTTGCCCCCTCCCCCTCCTTCTGTCCCCTCCCTTTCTTCTG  
GCTTGAGGTAGGGGCTCTTAAGGTACAGAACTCCACAAACCTTCCAAATCTGGAGGAG  
GGCCCCCATAACATTACAATTCCTCCCTTGCTCGGCGGTGGATTGCGAAGGCCCGTCCCT

CCACGGGTGTGGGCGCTGGCAGTCTCAGCCTCCCTCCACGGTCACCTTCAACGCCCAG  
ACACTCCCTTCTCCACCTTAGTTGGTTACAGGGTGAGTGAGATAACCAATGCCAACT  
TTTTGAAGTCTAATTTTTGAGGGGTGAGCTCATTTCTCTAGTGTCTAAAACCTGGT  
ATGGGTTTGGCCAGCGTCATGGAAAGATGTGGTTACTGAGATTTGGGAAGAAGCATGA  
AGCTTTGTGTGGGTTGGAAGAGACTGAAGATATGGGTTATAAAATGTTAATTCTAATTG  
CATACGGATGCCTGGCAACCTTGCCCTTGAGAATGAGACAGCCTGCGCTTAGATTTTAC  
CGGTCTGTAAAATGGAAATGTTGAGGTCACCTGGAAAGCTTTGTTAAGGAGTTGATGTT  
TGCTTTCCTTAACAAGACAGCAAAACGTAAACAGAAATTGAAAACCTGAAGGATATTT  
CAGTGTGATGGACTTCCTCAAAATGAAGTGCTATTTTCTTATTTTAATCAAATAACTA  
GACATATATCAGAAACTTTAAAATGTAAAAGTTGTACACTTTCAACATTTTATTACGAT  
TATTATTCAGCAGCACATTCTGAGGGGGGAACAATTCACACCACCAATAATAACCTGG  
TAAGATTTTCAAGAGGTAAAGAAGGTGGAATAATTGACGGGGAGATAGCGCCTGAAAT  
AAACAAAATATGGGCATGCATGCTAAAGGGAAAATGTGTGCAGGTCTACTGCATTAAA  
TCCTGTGTGCTCCTCTTTTGGATTTACAGAAATGTGTCAAATGTAAATCTTTCAAAGCC  
ATTTAAAATATTTCACTTTAGTTCTCTGTGAAGAAGAGGAGAAAAGCAATCCTCCTGAT  
TGTATTGTTTTAAACTTTAAGAATTTATCAAAATGCCGGTACTTAGGACCTAAATTTAT  
CTATGTCTGTACATCGCTAAAATGATATTGGTCTTTGAATTTGGTATACATTTATTCTGT  
TCACTATCACAAAATCATCTATTTATAGAGGAATAGAAGTTTATATATATATAATAC  
CATATTTTAAATTCACAAATAAAAAATTCAAAGTTTTGTACAAAATTATATGGATTTT  
GTGCCTGAAAATAATAGAGCTTGAGCTGTCTGAACTATTTTACATTTTATGGTGTCTCA  
TAGCCAATCCACAGTGTA AAAATTCA

Figure 58

MAEEEAPKKSRAAGGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRLRLARQLLLL  
WLLEAPLLLGVRAQAAGQGPGQGPQGPQPPPPQQQSGQQYNGERGIVPDHGYCQPI  
SIPLCDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCTVL  
EQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHGAGELCVGQNTSDKGTPTP  
SLLPEFWTSNPQHGGGGHRRGGFPGGAGASERGFSCPRALKVPSYLNHFLGEKDCGAPC  
EPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMMRRFSYPERPIIFLSGCT  
AVAVAYIAGFLLDRVVCNDKFAEDGARTVAQGTKKEGCTILFMMLYFFSMASIIWW  
VILSLTWFLAAGMKWGHEAIEANSQYFHLLAAWAVPAIKTTITLALGQVDGDVLSGVCFVG  
LNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRITMKHDKTEKLEKLMVRIGVFSV  
LYTVPATIVIACYFYEQA  
FRDQWERSWVAQSCKSYAIPCPHLQAGGGAPPPHPPMSPDFTVFMKYLMTLIVGITSQFWI  
WSGKTLNSW RKFYTRLTNSKQGETTV

Figure 59

CGAGTAAAGTTTGCAAAGAGGGCGCGGGAGGGCGGCAGCCGCAGCGAGGAGGCGGGCGGG  
GAAGAAGCGCAGTCTCCGGGTTGGGGGCGGGGGCGGGGGGGCGCCAAGGAGCCGGG  
TGGGGGGCGGGCGCCAGCATGCGGCCCGCAGCGCCCTGCCCGCCTGCTGCTGCCGC  
TGCTGCTGCTGCCCGCCGCGGGCGGCCAGTTCCACGGGGAGAAGGGCATCTCCAT  
CCCGGACCACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCCTACA  
ACCAGACCATCATGCCCAACCTTCTGGGCCACACGAACCAGGAGGACGCAGGCCTAGA  
GGTGCACCAGTTCTATCCGCTGGTGAAGGTGCAGTGCTCGCCCGAACTGCGCTTCTTCC  
TGTGCTCCATGTACGCACCCGTGTGCACCGTGCTGGAACAGGCCATCCCGCCGTGCCGC  
TCTATCTGTGAGCGCGCGCCAGGGCTGCGAAGCCCTCATGAACAAGTTCGGTTTTCA  
GTGGCCCGAGCGCCTGCGCTGCGAGCACTTCCCGCGCCACGGCGCCGAGCAGATCTGC

CGGGACTGCAGCCGGGTGCCGGGGGCACCCCGGGTGGCCCGGGCGGGCGGGCGCTC  
CCCCGCGCTACGCCACGCTGGAGCACCCCTTCCACTGCCCCGCGCGTCTCAAGGTGCCA  
TCCTATCTCAGCTACAAGTTTCTGGGCGAGCGTGATTGTGCTGCGCCCTGCGAACCTGC  
GCGGCCCCGATGGTTCCATGTTCTTCTCACAGGAGGAGACGCGTTTCGCGCGCCTCTGGA  
TCCTCACCTGGTTCGGTGCTGTGCTGCGCTTCCACCTTCTTCACTGTCACCACGTAATTGG  
TAGACATGCAGCGCTTCCGCTACCCAGAGCGGCCTATCATTTTTTCTGTGCGGGCTGCTAC  
ACCATGGTGTTCGGTGGCCTACATCGCGGGCTTCGTGCTCCAGGAGCGCGTGGTGTGCA  
ACGAGCGCTTCTCCGAGGACGGTTACCGCACGGTGGTGCAGGGCACCAAGAAGGAGG  
GCTGCACCATCCTCTTCATGATGCTCTACTTCTTCAGCATGGCCAGCTCCATCTGGTGG  
GTCATCCTGTGCTCACCTGGTTCTTGGCAGCCGGCATGAAGTGGGGCCACGAGGCCA  
TCGAGGCCAACTCTCAGTACTTCCACCTGGCCGCTGGGGCCGTGCCGGCCGTCAAGAC  
CATCACCATCCTGGCCATGGGCCAGATCGACGGCGACCTGCTGAGCGGCGTGTGCTTC  
GTAGGCCTCAACAGCCTGGACCCGCTGCGGGGCTTCGTGCTAGCGCCGCTCTTCGTGTA  
CCTGTTTCATCGGCACGTCCTTCTCCTGGCCGGCTTCGTGTCGCTCTTCCGCATCCGCAC  
CATCATGAAGCACGACGGCACCAAGACCGAAAAGCTGGAGCGGCTCATGGTGC GCAT  
CGGCGTCTTCTCCGTGCTCTACACAGTGCCCGCCACCATCGTCATCGCTTGCTACTTCTA  
CGAGCAGGCCTTCCGCGAGCACTGGGAGCGCTCGTGGGTGAGCCAGCACTGCAAGAGC  
CTGGCCATCCCGTGCCCGGCGCACTACACGCGCGCATGTGCGCCGACTTCACGGTCTA  
CATGATCAAATACCTCATGACGCTCATCGTGGGCATCACGTGCGGCTTCTGGATCTGGT  
CGGGCAAGACGCTGCACTCGTGGAGGAAGTTCTACTCGCCTACCAACAGCCGACA  
CGGTGAGACCACCGTGTGAGGGACGCCCCAGGCCGAACCGCGCGGCGCTTTCCTCC  
GCCCCGGGTGGGGCCCCCTACAGACTCCGTATTTTATTTTTTAAATAAAAAACGATCGA  
AACCATTTCACTTTTAGGTTGCTTTTTAAAGAGAACTCTCTGCCCAACACCCCC

Figure 60

MRPRSALPRLLLPLLLLPAAGPAQFHGEKGISIPDHGFCQPISIPLCIDIAYNQTIMPNLLGHT  
NQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCTVLEQAIPPCRSICERARQGCEALM  
NKGFGQWPERLRCEHFPRHGAEQICVQGNHSEDGAPALLTAPPPGLQPGAGGTPGGP  
GGAPPRYATLEHPFHCPRVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEETRFARL  
WILTWSVLCCASTFFTVTTYLVDMQRFRYPRIIFLSGCTMVSVAYIAGFVLQERVVCN  
ERFSEDEGYRTVVQGTKKEGCTILFMMLYFFSMASIIWWVILSLTWFLAAGMKWGHAEIA  
NSQYFHLAAWAVPAVKTTITLAMQIDGDLISGVCFVGLNSLDPLRGFVLAPLFVYLFITGS  
FLLAGFVSLFRIRTIMKHDGKTEKLERLMVRIGVFSVLYTVPATIVACYFYEQAFREHW  
ERSWVSQHCKSLAIPCAHYTPRMSPDFTVYMIKYLMTLIVGITSGFVIWSGKTLHSWRKF  
YTRLTNSRHGETTV

Figure 61

GCCGCTCCGGGTACCTGAGGGACGCGCGGCGCCCGCGGCAGGCGGTGCAGCCCCCCC  
CCACCCCTTGAGGCCAGGCGCCGGGGTCTGAGGATAGCATTCTCAAGACCTGACTTA  
TGGAGCACTTGTAACCTGAGATATTTAGTTGAAGGAAGAAATAGCTCTTCTCCTAAGA  
TGAATCTGTGGTTTGGGAATGTGGTTGATCAACTTGATATGTTGGCCAAATGTGCCCC  
ATGTAATAAAATGAAAAGAAGAGACAAGATGATGTCATTTTCCCATATTGTGAAACCA  
AAAACAAACGCCTTTTGTGAGACCAAGCTAACAAACCTCTGACGGTGCAGAGAGTATT  
TAACTGTTTGAAGAATTTAACAGTAAGATACAGAAGAAGTACCTTCGAGCTGAGACCT  
GCAGGTGTATAAATATCTAAAATACATATTGAATAGGCCTGATCATCTGAATCTCCTTC  
AGACCCAGGAAGGATGGCTATGACTTGGATTGTCTTCTCTTGGCCCTTGACTGTGT  
TCATGGGGCATATAGGTGGGCACAGTTTGTCTTCTGTGAACCTATTACCTTGAGGATG  
TGCCAAGATTTGCCTTATAATACTACCTTCATGCCTAATCTTCTGAATCATTATGACCAA

GGATTTCCGGCCTTTTCTTTGTGCACTCTACGCTCCTATTTGTATGGAATATGGACGTGT  
CACACTTCCCTGTCGTAGGCTGTGTGTCAGCGGGCTTACAGTGAGTGTTCCGAAGCTCATGG  
AGATGTTTGGTGTTCCTTGGCCTGAAGATATGGAATGCAGTAGGTTCCCAGATTGTGAT  
GAGCCATATCCTCGACTTGTGGATCTGAATTTAGCTGGAGAACCAACTGAAGGAGCCC  
CAGTGGCAGTGCAGAGAGACTATGGTTTTTGGTGTCCCCGAGAGTTAAAAATTGATCCT  
GATCTGGGTTATTCTTTTCTGCATGTGCGTGATTGTTACCTCCTTGTCCAAATATGTAC  
TTCAGAAAGAGAAGAACTGTCATTGCTCGCTATTTTCATAGGATTGATTTCAATCATTG  
CCTCTCGGCCACATTGTTTACTTTTTTAACTTTTTTGATTGATGTCACAAGATTCCGTTA  
TCCTGAAAGGCCTATTATATTTTATGCAGTCTGCTACATGATGGTATCCTTAATTTTCTT  
CATTGGATTTTTGCTTGAAGATCGAGTAGCCTGCAATGCATCCATCCCTGCACAATATA  
AGGCTTCCACAGTGACACAAGGATCTCATAATAAAGCCTGTACCATGCTTTTTATGATA  
CTCTATTTTTTACTATGGCTGGCAGTGTATGGTGGGTAATTCTTACCATCACATGGTTT  
TTAGCAGCTGTGCCAAAGTGGGGTAGTGAAGCTATTGAGAAGAAAGCATTGCTGTTT  
ACGCCAGTGCATGGGGCATCCCCGGAACCTCTAACCATCATCCTTTTAGCGATGAATAA  
AATTGAAGGTGACAATATTAGTGGCGTGTGTTTTGTTGGCCTCTACGATGTTGATGCAT  
TGAGATATTTTGTCTTGTCTCCCTCTGCCTGTATGTGGTAGTTGGGGTTTCTCTCCTCTT  
AGCTGGCATTATATCCCTAAACAGAGTTCGAATTGAGATTCCATTAGAAAAGGAGAAC  
CAAGATAAATTAGTGAAGTTTATGATCCGGATCGGTGTTTTTACGATTCTTTATCTCGT  
ACCACTCTTGGTTGTAATTGGATGCTACTTTTATGAGCAAGCTTACCGGGGCATCTGGG  
AAACAACGTGGATACAAGAACGCTGCAGAGAATATCACATTCCATGTCCATATCAGGT  
TACTCAAATGAGTCGTCCAGACTTGATTCTCTTTCTGATGAAATACCTGATGGCTCTCA  
TAGTTGGCATTCCCTCTGTATTTTGGGTTGGAAGCAAAAAGACATGCTTTGAATGGGCC  
AGTTTTTTTTCATGGTCGTAGGAAAAAAGAGATAGTGAATGAGAGCCGACAGGTA  
AGGAACCTGATTTTGTCTAGTCTCTCCTGAGGGATCCAAATACTCCTATCATAAGAAAG  
TCAAGGGGAACCTTCCACTCAAGGAACATCCACCCATGCTTCTTCAACTCAGCTGGCTAT  
GGTGGATGATCAAAGAAGCAAAGCAGGAAGCATCCACAGCAAAGTGAGCAGCTACCA  
CGGCAGCCTCCACAGATCACGTGATGGCAGGTACACGCCCTGCAGTTACAGAGGAATG  
GAGGAGAGACTACCTCATGGCAGCATGTCACGACTAACAGATCACTCCAGGCATAGTA  
GTTCTCATCGGCTCAATGAACAGTCAAGACATAGCAGCATCAGAGATCTCAGTAATAA  
TCCCATGACTCATATCACACATGGCACCAGCATGAATCGGGTTATTGAAGAAGATGGA  
ACCAGTGCTTAATTTGTCTTGTCTAAGGTGGAAATCTTGTGCTGTTTAAAAAGCAGATT  
TTATTCTTTGCCTTTTGCATGACTGATAGCTGTACTCACAGTTAACATGCTTTCAGTCAA  
GTACAGATTGTGTCCACTGGAAAGGTAAATGATTGCTTTTTTATATTGCATCAAACCTTG  
GAACATCAAGGCATCCAAAACACTAAGAATTCTATCATCAAAAAATAATTTCGTCTTTC  
TAGGTTATGAAGAGATAATTATTTGTCTGGTAAGCATTTTTATAAACCCACTCATTTTAT  
ATTTAGAAAAATCCTAAATGTGTGGTGAAGTGTCTTGTAGTGAACCTTTCATATACTATAA  
ACTAGTTGTGAGATAACATTCTGGTAGCTCAGTTAATAAAACAATTTTCAAGATTAAAG  
AAATTTTCTATGCAAGGTTTACTTCTCAGATGAACAGTAGGACTTTGTAGTTTTATTTC  
ACTAAGTGAAAAAAGAACTGTGTTTTTAACTGTAGGAGAATTTAATAAATCAGCAAG  
GGTATTTTAGCTAATAGAATAAAAGTGCAACAGAAGAATTTGATTAGTCTATGAAAGG  
TTCTCTTAAATTTCTATCGAAATAATCTTCATGCAGAGATATTCAGGGTTTGGATTAGC  
AGTGGAATAAAGAGATGGGCATTGTTTCCCTATAATTGTGCTGTTTTTATAACTTTTGT  
AAATATTACTTTTTCTGGCTGTGTTTTTATAACTTATCCATATGCATGATGGAAAAATTT  
TAATTTGTAGCCATCTTTTCCCATGTAATAGTATTGATTCATAGAGAACTTAATGTTCAA  
AATTTGCTTTGTGGAGGCATGTAATAAGATAAACATCATACATTATAAGGTAACCACA  
ATTACAAAATGGCAAAACA

Figure 62

MAMTWIVFSLWPLTVFMGHIGGHSLSFCEPITLRMCQDLPYNTTFMPNLLNHYDQQTAAL

WPEDMECSRFPDCDEPYPRVLVDNLAGEPTGAPVAVQRDYGFWCPRELKIDPDLGYSFL  
HVRDCSPPCPNMYFRREELSFARYFIGLISIICLSATLFTFLTFLIDVTRFRYPERPIFYAVCY  
MMVSLIFFIGFLLIEDRVACNASIPAQYKASTVTQGSNKA CTMLFMILYFFTMAGSVWWVI  
LTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLTILLAMNKIEGDNISGVCFVGLYDV  
DALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIEIPLEKENQDKLVKFMIRIGVFSILYL VPL  
LVVIGCYFYEQAYRGIWETT WIQERCREYHPCPYQVTQMSRPDLILFLMKYLMALIVGIPS  
VFWVGSKKTCFEWASFFHGRRKKEIVNESRQVLQEPDFAQSLLRDPNTPIRKSRGTSTQGT  
STHASSTQLAMVDDQRSKAGSIHSKVSSYHGSLSRSDGRYTPCSYRGMEERLPHGSMR  
LTDHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTS MNRVIEEDG TSA

Figure 63

GCTGCGCAGCGCTGGCTGCTGGCTGGCCTCGCGGAGACGCCGAACGGACGCGGCCGGC  
GCCGGCTTGTGGGCTCGCCGCCTGCAGCCATGACCCTCGCAGCCTGTCCCTCGGCCTCG  
GCCCCGGACGTCTAAAATCCCACACAGTCGCGCGCAGCTGCTGGAGAGCCGGCCGCTG  
CCCCCTCGTCGCCGCATCACACTCCCGTCCCGGGAGCTGGGAGCAGCGCGGGCAGCCG  
GCGCCCCCGTGCAAACCTGGGGGTGTCTGCCAGAGCAGCCCCAGCCGCTGCCGCTGCTA  
CCCCCGATGCTGGCCATGGCCTGGCGGGGCGCAGGGCCGAGCGTCCCGGGGGCGCCCCG  
GGGGCGTCGGTCTCAGTCTGGGGTTGCTCCTGCAGTTGCTGCTGCTCCTGGGGCCGGCG  
CGGGGCTTCGGGGACGAGGAAGAGCGGGCGCTGCGACCCCATCCGCATCTCCATGTGCC  
AGAACCTCGGCTACAACGTGACCAAGATGCCCAACCTGGTTGGGCACGAGCTGCAGAC  
GGACGCCGAGCTGCAGCTGACAACTTTCACACCGCTCATCCAGTACGGCTGCTCCAGC  
CAGCTGCAGTTCTTCTTTGTTCTGTTTATGTGCCAATGTGCACAGAGAAGATCAACAT  
CCCCATTGGCCCATGCGGGCGGCATGTGTCTTTCAGTCAAGAGACGCTGTGAACCCGTCC  
TGAAGGAATTTGGATTTGCCTGGCCAGAGAGTCTGAACTGCAGCAAATTTCCACCACA  
GAACGACCACAACCACATGTGCATGGAAGGGCCAGGTGATGAAGAGGTGCCCTTACCT  
CACAAAACCCCATCCAGCCTGGGGAAGAGTGTCACTCTGTGGGAACCAATTCTGATC  
AGTACATCTGGGTGAAAAGGAGCCTGAACTGTGTGCTCAAGTGTGGCTATGATGCTGG  
CTTATACAGCCGCTCAGCCAAGGAGTTCAGTATCTGGATGGCTGTGTGGGCCAGCC  
TGTGTTTCATCTCCACTGCCTTCACAGTACTGACCTTCCTGATCGATTCTTCTAGGTTTT  
CCTACCCTGAGCGCCCCATCATATTTCTCAGTATGTGCTATAATATTTATAGCATTGCTT  
ATATTGTCAGGCTGACTGTAGGCCGGGAAAGGATATCCTGTGATTTTGAAGAGGCAGC  
AGAACCTGTTCTCATCCAAGAAGGACTTAAGAACACAGGATGTGCAATAATTTTCTTGC  
TGATGTACTTTTTTGAATGGCCAGCTCCATTTGGTGGGTATTCTGACACTCACTTGGT  
TTTTGGCAGCAGGACTCAAATGGGGTCATGAAGCCATTGAAATGCACAGCTCTTATTT  
CACATTGCAGCCTGGGCCATCCCCGCAGTGAAAACCATTTGTCATCTTGATTATGAGACT  
GGTGGATGCAGATGAACTGACTGGCTTGTGCTATGTTGGAAACCAAAATCTCGATGCC  
CTCACCGGGTTCGTGGTGGCTCCCCTCTTACTTATTTGGTCAATTGGAACCTTTGTTCA  
GCTGCAGGTTTGGTGGCCTTGTTCAAAATTCGGTCAAATCTTCAAAGGATGGGACAA  
AGACAGACAAGTTAGAAAGACTGATGGTCAAGATTGGGGTGTCTCAGTACTGTACAC  
AGTTCCTGCAACGTGTGTGATTGCCTGTTATTTTTATGAAATCTCCAACCTGGGCACTTT  
TCGGTATTCTGCAGATGATTCCAACATGGCTGTTGAAATGTTGAAAACCTTTATGTCTTT  
GTTGGTGGGCATCACTTCAGGCATGTGGATTGGTCTGCCAAAAGTCTTCACACGTGGC  
AGAAGTGTTCACACAGATTGGTGAATTCTGGAAAGGTAAAGAGAGAGAAGAGAGGAA  
ATGGTTGGGTGAAGCCTGGAAAAGGCAGTGAGACTGTGGTATAAGGCTAGTCAGCCTC  
CATGCTTTCTTCATTTTGAAGGGGGGAATGCCAGCATTTTGGAGGAAATTCTACTAAAA  
GTTTTATGCAGTGAATCTCAGTTTGAACAACTAGCAACAATTAAGTGACCCCCGTCAA  
CCCCTGCCTCCACCCCGACCCAGCATCAAAAAACCAATGATTTTGTCTGCAGACTTT  
GGAATGATCAAAAATGGAAAAGCCAGTTAGAGGCTTTCAAAGCTGTGAAAAATCAAA  
ACGTTGATCACTTTAGCAGGTTGCAGCTTGGAGCGTGGAGGTCTGCCTAGATTCCAGG  
AAGTCCAGGGCGATACTGTTTTCCCTGCAGGGTGGGATTTGAGCTGTGAGTTGGTAAC



TTCAGATAGCAAAGCAATCTATAAACACTGGAAACGCTGGGTTTCAGAAAAGTGTTACA  
AGAGTTTTATAGTTTGGCTGATGTAACATAAACATCTTCTGTGGTGCGCTGTCTGCTGTT  
TAGAACTTTGTGGACTGCACTCCCAAGAAGTGGTGTAGAAATCTTTCAGTGCCTTTGTC  
ATAAAACAGTTATTTGAACAAACAAAAGTACTGTACTCACACACATAAGGTATCCAGT  
GGATTTTTCTTCTCTGTCTTCTCTTAAATTTCAACATCTCTCTTCTGGCTGCTGCTG  
TTTTCTTCATTTTATGTTAATGACTCAAAAAAGGTATTTTTATAGAATTTTTGTACTGCA  
GCATGCTTAAAGAGGGGAAAAGGAAGGGTGATTACATTTCTGACAATCACTTAATTCA  
GAGGAAAATGAGATTTACTAAGTTGACTTACCTGACGGACCCCAGAGACCTATTGCAT  
TGAGCAGTGGGGACTTAATATATTTTACTTGTGTGATTGCATCTATGCAGACGCCAGTC  
TGGAAGAGCTGAAATGTAAAGTTTCTTGCAACTTTGCATTACACAGATTAGCTGTGT  
AATTTTTGTGTGTCAATTACAATTAAGGCACATTGTTGGACCATGACATAGTATACTC  
AACTGACTTTAAACTATGGTCAACTTCAACTTGCATTCTCAGAATGATAGTGCCTTTA  
AAATTTTTTATTTTTTAAAGCATAAGAATGTTATCAGAATCTGGTCTACTTAGGACAA  
TGGAGACTTTTTCAGTTTTATAAAGGGAAGTGGAGACAGCTAATCCAAGTACTTGGTGC  
TGTAATTGTTTCTAGTAATTGGCAAAGGCTCCTTGTAAGATTTCACTGGAGGCAGTGT  
GGCCTGGAGTATTTATATGGTGCTTAATGAATCTCCAGAATGCCAGCCAGAAGCCTGAT  
TGGTTAGTAGGGAATAAAGTGTAGACCATATGAAATGAACTGCAAACTCTAATAGCCC  
AGGTCTTAATTGCCTTTAGCAGAGGTATCCAAAGCTTTTAAAATTTATGCATACGTTCT  
TCACAAGGGGGTACCCCCAGCAGCCTCTCGAAAATTGCACTTCTCTTAAACTGTAAGT  
GGCCTTTCTCTTACCTTGCCTTAGGCCTTCTAATCATGAGATCTTGGGGACAAATTGACT  
ATGTCACAGGTTGCTCTCCTTGTAAGTCAATACCTGTCTGCTTCAGCAACTGCTTTGCAAT  
GACATTTATTTATTAATTCATGCCTTAAAAAATAGGAAGGGAAGCTTTTTTTTTCTTT  
TTTTTTTTTCAATCACACTTTGTGGAAAAACATTTCCAGGGACTCAAAATTCAAAAA  
GGTGGTCAAATTCTGGAAGTAAGCATTTCTCTTTTTTAAAAATTTGGTTTGAGCCTTAT  
GCCCATAGTTTGACATTTCCCTTTCTTCTTTCTTTTTTGTGTTTGTGGTTCTTGAGCTC  
TCTGACATCAAGATGCATGTAAAGTCGATTGTATGTTTTGAAGGCAAAGTCTTGGCTTT  
TGAGACTGAAGTTAAGTGGGCACAGGTGGCCCCCTGCTGCTGTGCCAGTCTGAGTACC  
TTGGCTAGACTCTAGGTCAGGCTCCAGGAGCATGAGAATTGATCCCCAGAAGAACCAT  
TTAACTCCATCTGATACTCCATTGCCTATGAAATGTAAAATGTGAACTCCCTGTGCTG  
CTTGTAGACAGTTCCCATAACTGTCCACGGCCCTGGAGCACGCACCCAGGGGCAGAGC  
CTGCCCTTACTCACGCTCTGCTCTGGTGTCTTGGGAGTTGTGCAAGGACTCTGGCCCAG  
GCAGGGGAAGGAAGACCAGGCGGTAGGGGACTGGTCTTGTGTTAGAGTATAGAGGTT  
TGTAATGCAGTTTTCTTCATAATGTGTGAGTGATTGTGTGACCAAGGCAGCATCTAGCA  
GAAAGCCAGGCATGGAGTAGGTGATCGATACTTGTCAATGACTAAATAATAACAATAA  
AAGAGCACTTGGGTGAATCTGGGCACCTGATTTCTGAGTTTTGAGTTCTGGAGCTAGTG  
TTTTGACAATGCTTTGGGTTTTGACATGCCTTTTCCACAAATCTCTTGCCTTTTCAGGGC  
AAAGTGTATTTGATCAGAAGTGGCCATTTGGATTAGTAGCCTTAGCAATGCTACAGGGT  
TATAGGCCCTCTCCCTTTACATTCCAGACAATGGAGAGTGTTTATGGTTTCAGGAAA  
AGAATTTGTGGCTGAGGGGTGAGTTACAGTGACCTTCAATCAACTCCATCACTTCTT  
AAATCGGTATTTGTGTAATAAAAAATCAGTTATTTTATTTATGAGTGCCGACTGTAGTAAA  
GCCCTGAAATAGATAATCTCTGTTCTTCTAACTGATCTAGGATGGGGACGCACCCAGGT  
CTGCTGAACCTTACTGTTCTCTGCGAAAGGAGCAGGGACCTCTGGAATTTCCATCTGT  
TTCACTGTCTCCATTCCATAAATCTCTTCTGTGTGAGCCACCACCCAGCCTGGGTCT  
CTCTACTTTTAAACACATCTCTCATCCCTTTCCAGGACTTCCTTCCAAGTCAGTTACAGG  
TGGTTTTAACAGAAAGCATCAGCTCTGCTTCGTGACAGTCTCTGGAGAAATCCCTTAGG  
AAGACTATGAGAGTAGGCCACAAGGACATGGGCCACACATCTGCTTTGGCTTTGCCG  
GCAATTCAGGGCTTGGGGTATTCCATGTGACTTGTATAGGTATATTTGAGGACAGCATC  
TTGCTAGAGAAAAGGTGAGGGTTGTTTTCTTCTCTGAAACCTACAGTAAATGGGTAT  
GATTGTAGCTTCCCTCAGAAATCCCTTGGCCTCCAGAGATTAAACATGGTGCAATGGCAC  
CTCTGTCCAACCTCCTTTCTGGTAGATTCTTTCTCTGCTTCATATAGGCCAAACCTCA  
GGGCAAGGGAACATGGGGGTAGAGTGGTGCTGGCCAGAACCATCTGCTTGAGCTACTT

TGAAC TGGCAACTTACTTGGGCCTGAAACTGGAGAAGGGGTGACATTTTTTTAATTTCAG  
GAGATGCTTTCTGATTTTCCTCTCCCAGGTCACCTGTCTCACCTGCACTCTCCAAACTCAG  
GTTCCGGGAAGCTTGTGTGTCTAGATACTGAATTGAGATTCTGTTTCAGCACCTTTTAGC  
TCTATACTCTCTGGCTCCCCTCATCCTCATGGTCACTGAATTAATGCTTATTGTATTGA  
GAACCAAGATGGGACCTGAGGACACAAAGATGAGCTCAACAGTCTCAGCCCTAGAGG  
AATAGACTCAGGGATTTCACCAGGTCGGTGCAGTATTTGATTTCTGGTGAGGTGACCAC  
AGCTGCAGTTAGGAAGGGAGCCATTGAGCACAGACTTTGGAAGGAACCTTTTTTTTGT  
GTTTGTGTTGTTTGTGTTGTTTGTGTTGTTGAGACAGGGTCTTGCTCTGCTACCCAGG  
CTGGGGCGCAATGGCACGATCTTGGCTCACTGCAACCTCTGCCTCCTGGGTTC AAGTGA  
TTCTCCTGCCACAGCCTCCTGAGGAGCTGGGACTACAGGTGCGTGCTACCACGCCCAG  
CTACTTCTGTATTTTTAGTAGAGACGGGGTTTCACTGTGTTGGCCAGGCTGGTCTCGAA  
CTCCTGACCTCATGATCTGCCCGCCTCAGCCTCCCAAAGTGCTGGGATTACAAGTGTGA  
GCCACCACACCTGGCCTGGAAGGAACCTCTTAAAATCAGTTTACGTCTTGTATTTGTT  
CTGTGATGGAGGACACTGGAGAGAGTTGCTATTCCAGTCAATCATGTGCGAGTCACTGG  
ACTCTGAAAATCCTATTGGTTCCTTTATTTTATTTGAGTTTAGAGTTCCCTTCTGGGTTT  
GTATTATGTCTGGCAAATGACCTGGGTTATCACTTTTCTCCTCCAGGGTTAGATCATAGAT  
CTTGAAACTCCTTAGAGAGCATTGTTGCTCCTACCAAGGATCAGATACTGGAGCCCCAC  
ATAATAGATTTCACTTCACTCTAGCCTACATAGAGCTTTCTGTTGCTGTCTCTTGCCATG  
CACTTGTGCGGTGATTACACACTTGACAGTACCAGGAGACAAATGACTTACAGATCCC  
CCGACATGCCTCTTCCCCTTGGCAAGCTCAGTTGCCCTGATAGTAGCATGTTTCTGTTTCT  
TGATGTACCTTTTTTCTCTTCTTCTTGCATCAGCCAATTCCCAGAATTCCCCAGGCAA  
TTTGTAGAGGACCTTTTTTGGGGTCTATATGAGCCATGTCCTCAAAGCTTTTAAACCTC  
CTTGCTCTCCTACAATATTAGTACATGACCACTGTCTATCTAGAAAGGCTTCTGAAAAG  
AGGGGCAAGAGCCACTCTGCGCCACAAAGGTTGGATCCATCTTCTCTCCGAGGTTGTG  
AAAGTTTTCAAATTGTAATAAGGCTGGGGCCCTGACTTGGCTGTGGGCTTTGGGAGG  
GGTAAGCTGCTTTCTAGATCTCTCCAGTGAGGCATGGAGGTGTTTCTGAATTTTGTCT  
ACCTCACAGGGATGTTGTGAGGCTTGAAAAGGTCAAAAATGATGGCCCCCTTGAGCTC  
TTTGTAAGAAAGGTAGATGAAATATCGGATGTAATCTGAAAAAAGATAAAATGTGAC  
TTCCCCTGCTCTGTGCAGCAGTCGGGCTGGATGCTCTGTGGCNTTTCTTGGGTCCTCATG  
CCACCCACAGCTCCAGGAACCTTGAAGCCAATCTGGGGACTTTCAGATGTTTGACAA  
AGAGGTACCAGGCAAACTTCTGCTACACATGCCCTGAATGAATTGCTAAATTTCAA  
GGAAATGGACCCTGCTTTTAAGGATGTACAAAAGTATGTCTGCATCGATGTCTGTACTG  
TAAATTTCTAATTTATCACTGTACAAAGAAAACCCCTTGCTATTTAATTTGTATTAAAG  
GAAAATAAAGTTTTGTTTGTAAAAA

Figure 64

MAWRGAGPSVPGAPGGVGLSLGLLLQLLLLGPARGFGDEEERRCDPIRISM CQN LGYNV  
TKMPNLVGHELQTD AELQLTTF TPLIQYGCSSQLQFFLCSVYVPMCTE KINIPGPCGGMCL  
SVKRRCEPVLKEFGFAWPESLNC SKFPPQNDHNHMCMEGPGDEEVPLPHKTPIQPGECHS  
VG TNSDQYI WVKRSLNCVLKCGYDAGLYSRSAKEFTDIWMAVWASLCFISTAFTVLTFLID  
SSRFSYPERPIIFLSMCYNIYSIAYTVRLTVGRERISCD FEEAAEPVLIQEG LKNTGCAIFLLM  
YFFGMASSIWWVILTLTWFLAAGLKWGHEA IEMHSSYFHIAAWAIPAVKTTIVILIMRLVDA  
DELTGLCYVGNQNLDA LTGFVVAPLFTYL VIGTLFIAAGLVALFKIRSNLQKDGTKTDKLE  
RLMVKIGVFSVLYTVPATCVIACYFYEISN WALFRYSADDSNMAVEMLKTFM SLLVGIT  
SGMWIWSAKSLHTWQKCSNRLVNSGKVKREKRNGWVKPGKGSETVV



Figure 65

ACCCAGGGACGGAGGACCCAGGCTGGCTTGGGGACTGTCTGCTCTTCTCGGCGGGAGC  
CGTGGAGAGTCCTTTCCCTGGAATCCGAGCCCTAACCGTCTCTCCCCAGCCCTATCCGG  
CGAGGAGCGGAGCGCTGCCAGCGGAGGCAGCGCCTTCCCGAAGCAGTTTATCTTTGGA  
CGGTTTTCTTTAAAGGAAAAACGAACCAACAGGTTGCCAGCCCCGGCGCCACACACGA  
GACGCCGGAGGGAGAAGCCCCGGCCCGGATTCTCTGCCTGTGTGCGTCCCTCGCGGG  
CTGCTGGAGGCGAGGGGAGGGAGGGGGCGATGGCTCGGCCTGACCCATCCGCGCCGC  
CCTCGCTGTTGCTGCTGCTCCTGGCGCAGCTGGTGGGCGGGGCGGCCGCGCTCCAA  
GGCCCCGGTGTGCCAGGAAATCACGGTGGCCATGTGCCGCGGCATCGGCTACAACCTG  
ACGCACATGCCCAACCAGTTCAACCACGACACGCAGGACGAGGCGGGCCTGGAGGTG  
CACCAGTTCTGGCCGCTGGTGGAGATCCAATGCTCGCCGACCTGCGCTTCTTCCTATG  
CACTATGTACACGCCCATCTGTCTGCCCCACTACCACAAGCCGCTGCCGCCCTGCCGCT  
CGGTGTGCGAGCGCGCCAAGGCCGGCTGCTCGCCGCTGATGCGCCAGTACGGCTTCGC  
CTGGCCCGAGCGCATGAGCTGCGACCGCCTCCCGGTGCTGGGCCGCGACGCCGAGGTC  
CTCTGCATGGATTACAACCGCAGCGAGGCCACCACGGCGCCCCCAGGCCTTTCCCAG  
CCAAGCCCAACCTTCCAGGCCCGCCAGGGGCGCCGGCCTCGGGGGGCGAATGCCCCGC  
TGGGGGCCCCGTTTCGTGTGCAAGTGTGCGAGCCCTTCGTGCCCATCTGAAGGAGTCAC  
ACCCGCTCTACAACAAGGTGCGGACGGGCCAGGTGCCCAACTGCGCGGTACCCTGCTA  
CCAGCCGTCTTTCAGTGCCGACGAGCGCACGTTTCGCCACCTTCTGGATAGGCCTGTGGT  
CGGTGCTGTGCTTCATCTCCACGTCCACCACAGTGGCCACCTTCCTCATCGACATGGAC  
ACGTTCCGCTATCCTGAGCGCCCCATCATCTTCCTGTGAGCCTGCTACCTGTGCGTGTG  
GCTGGGCTTCCTGGTGCCTGCTGGTGTGGGCCATGCCAGCGTGGCCTGCAGCCGCGAG  
CACAACCACATCCACTACGAGACCACGGGCCCTGCACTGTGCACCATCGTCTTCCTCCT  
GGTCTACTTCTTCGGCATGGCCAGCTCCATCTGGTGGGTCATCCTGTGCTCACCTGGTT  
CCTGGCCGCCGCGATGAAGTGGGGCAACGAGGCCATCGCGGGCTACGGCCAGTACTTC  
CACCTGGCTGCGTGGCTCATCCCCAGCGTCAAGTCCATCACGGCACTGGCGCTGAGCTC  
CGTGGACGGGGACCCAGTGGCCGGCATCTGCTACGTGGGCAACCAGAACCTGAACTCG  
CTGCGGCGCTTCGTGCTGGGCCCCGCTGGTGTCTACCTGCTGGTGGGCACGCTCTTCCT  
GCTGGCGGGCTTCGTGTGCTCTTCCGCATCCGCAGCGTCATCAAGCAGGGCGGCACC  
AAGACGGACAAGCTGGAGAAGCTCATGATCCGCATCGGCATCTTCACGCTGCTCTACA  
CGGTCCCCGCCAGCATTGTGGTGGCCTGCTACCTGTACGAGCAGCACTACCGCGAGAG  
CTGGGAGGCGGCGCTCACCTGCGCCTGCCCGGGCCACGACACCGGCCAGCCGCGCGCC  
AAGCCCGAGTACTGGGTGCTCATGCTCAAGTACTTCATGTGCCTGGTGGTGGGCATCAC  
GTCGGGCGTCTGGATCTGGTTCGGGCAAGACGGTGGAGTCGTGGCGGCGTTTCACCAGC  
CGCTGCTGCTGCCGCCCGCGGCGCGGCCACAAGAGCGGGGGCGCCATGGCCGAGGG  
GACTACCCCGAGGCGAGCGCCGCGCTCACAGGCAGGACCGGGCCGCGGGCCCCGCC  
GCCACCTACCACAAGCAGGTGTCCCTGTGCGACGTGTAGGAGGCTGCCGCCGAGGGAC  
TCGGCCGGAGAGCTGAGGGGAGGGGGGCGTTTTGTTTGGTAGTTTTGCCAAGGTCACT  
TCCGTTTACCTTCATGGTGTGTTGCCCCCTCCCGCGGCGACTTGGAGAGAGGGGAAGAG  
GGGCGTTTTTCGAGGAAGAACCCTGTCCCAGGTCTTCTCCAAGGGGCCAGCTCACGTGT  
ATTCTATTTTGCCTTTCTTACCTGCCTTCTTTATGGGAACCCTCTTTTAAATTTATATGTA  
T

Figure 66

MARPDPSAPPSLLLLLLAQLVGRAAAASKAPVCQETVPMCRGIGYNLTHMPNQFNHDTQ  
DEAGLEVHQFWPLVEIQCSPLDRFFLCTMYTPICLPDYHKPLPPCRSVCERAKAGCSPLMR  
QYGFAWPERMSCDRLPVLGRDAEVLCMDYNRSEATTAPPRFFPAKPTLPGPPGAPASGGE  
CPAGGPFVCKCREPFVPILKESHPLYNKVRTGQVPNCAPVCYQPSFSADERTFATFWIGLW  
SVLCFISTSTTVATFLIDMDTFRYPERPIFLSACYLCVSLGFLVRLVVGHASVACSREHNHII  
YETTGPALECTIVFLLVYFFGMASSIWWVILSLTWFLAAAMKWGNEAAGYGYFHLAAWL  
IPSVKSITALALSSVDGDPVAGICYVGNQNLNSLRRFVLGPLVLYLLVGTFLLAGFVSLFRI  
RSVIKQGGTKTDKLEKLMIRIGIFTLLYTVPASIVVACYLYEQHYRESWEAALTCACPGHD  
TGQPRAKPEYWVWMLKYFMCLVVGITSGVWWSGKTVESWRRFTSRCCCRPRRGHKSGG  
AMAAGDYPEASAALTGRTGPPGPAATYHKQVSLSHV

Figure 67

GCAGCTCCAGTCCCGGACGCAACCCCGGAGCCGTCTCAGGTCCCTGGGGGGAACGGTG  
GGTTAGACGGGGACGGGAAGGGACAGCGGCCTTCGACCGCCCCCGAGTAATTGACCC  
AGGACTCATTTTCAGGAAAGCCTGAAAATGAGTAAAATAGTGAAATGAGGAATTTGAA  
CATTTTATCTTTGGATGGGGATCTTCTGAGGATGCAAAGAGTGATTCATCCAAGCCATG  
TGGTAAAATCAGGAATTTGAAGAAAATGGAGATGTTTACATTTTTGTTGACGTGTATTT  
TTCTACCCCTCCTAAGAGGGGCACAGTCTCTTCACCTGTGAACCAATTACTGTTCCCAGA  
TGTATGAAAATGGCCTACAACATGACGTTTTTCCCTAATCTGATGGGTCATTATGACCA  
GAGTATTGCCGCGGTGGAAATGGAGCATTCTTCTCCTCTCGCAAATCTGGAATGTTTAC  
CAAACATTGAAACTTTCTCTGCAAAGCATTGTGACCAACCTGCATAGAACAAATTCAT  
GTGGTTCCACCTTGTGCGTAAACTTTGTGAGAAAGTATATTCTGATTGCAAAAAATTAAT  
TGACACTTTTGGGATCCGATGGCCTGAGGAGCTTGAATGTGACAGATTACAATACTGTG  
ATGAGACTGTTCTGTAACTTTTGATCCACACACAGAATTTCTTGGTCCTCAGAAGAAA  
ACAGAACAAGTCCAAAGAGACATTGGATTTTGGTGTCCAAGGCATCTTAAGACTTCTG  
GGGGACAAGGATATAAGTTTCTGGGAATTGACCAGTGTGCGCCTCCATGCCCAACAT  
GTATTTTAAAGTGATGAGCTAGAGTTTGCAAAAAGTTTTATTGGAACAGTTTCAATAT  
TTTGTCTTTGTGCAACTCTGTTTACATTCTTACTTTTTTAATTGATGTTAGAAGATTCA  
GATACCCAGAGAGACCAATTATATATTACTCTGTCTGTTACAGCATTGTATCTCTTATG  
TACTTCATTGGATTTTTGCTGGGCGATAGCACAGCCTGCAATAAGGCAGATGAGAAGC  
TAGAACTTGGTGACACTGTTGTCTTAGGCTCTCAAAATAAGGCTTGCACCGTTTTGTTC  
ATGCTTTTGTATTTTTTTCACAATGGCTGGCACTGTGTGGTGGGTGATTCTTACCATTACT  
TGGTTCTTAGCTGCAGGAAGAAAATGGAGTTGTGAAGCCATCGAGCAAAAAGCAGTGT  
GGTTTCATGCTGTTGCATGGGGAACACCAGGTTTCTGACTGTTATGCTTCTTGCTCTGA  
ACAAAGTTGAAGGAGACAACATTAGTGGAGTTTGCTTTGTTGGCCTTTATGACCTGGAT  
GCTTCTCGCTACTTTGTACTCTTGCCACTGTGCCTTTGTGTGTTTGTGGGCTCTCTCTTC  
TTTTAGCTGGCATTATTTCTTAAATCATGTTTCGACAAGTCATACAACATGATGGCCGG  
AACCAAGAAAACTAAAGAAAATTTATGATTCTGAATTGGAGTCTTCAGCGGCTTGTATC  
TTGTGCCATTAGTGACACTTCTCGGATGTTACGTCTATGAGCAAGTGAACAGGATTACC  
TGGGAGATAACTTGGGTCTCTGATCATTTGTCGTACGTACCATATCCCATGTCTTATCA  
GGCAAAAGCAAAAGCTCGACCAGAATTGGCTTTATTTATGATAAAATACCTGATGACA  
TTAATTGTTGGCATCTCTGCTGTCTTCTGGGTTGGAAGCAAAAAGACATGCACAGAATG  
GGCTGGGTTTTTTTAAACGAAATCGCAAGAGAGATCCAATCAGTGAAAGTCGAAGAGTA  
CTACAGGAATCATGTGAGTTTTTCTTAAAGCACAATTCTAAAGTTAAACACAAAAAGA  
AGCACTATAAACCAAGTTCACACAAGCTGAAGGTCATTTCCAAATCCATGGGAACCAG  
CACAGGAGCTACAGCAAATCATGGCACTTCTGCAGTAGCAATTACTAGCCATGATTAC  
CTAGGACAAGAACTTTGACAGAAATCCAAACCTCACCAGAAACATCAATGAGAGAG  
GTGAAAGCGGACGGAGCTAGCACCCCCAGGTTAAGAGAACAGGACTGTGGTGAACCT  
GCCTCGCCAGCAGCATCCATCTCCAGACTCTCTGGGGAACAGGTCGACGGGAAGGGCC

ATATTACTGACACTGGCCTGGCACAGAGCAACAATTTGCAGGTCCCCAGTTCTTCAGAA  
CCAAGCAGCCTCAAAGGTTCCACATCTCTGCTTGTTACCCAGTTTCAGGAGTGAGAAA  
AGAGCAGGGAGGTGGTTGTCATTTCAGATACTTGAAGAACATTTTCTCTCGTTACTCAGA  
AGCAAATTTGTGTTACACTGGAAGTGACCTATGCACTGTTTTGTAAGAATCACTGTTAC  
GTTCTTCTTTTGCACCTTAAAGTTGCATTGCCTACTGTTATACTGGAAAAAATAGAGTTC  
AAGAATAATATGACTCATTTACACAAAGGTTAATGACAACAATATACCTGAAAACAG  
AAATGTGCAGGTTAATAATATTTTTTTAATAGTGTGGGAGGACAGAGTTAGAGGAATC  
TTCCTTTTCTATTTATGAAGATTCTACTCTTGGTAAGAGTATTTAAGATGTACTATGCT  
ATTTTACCTTTTTGATATAAAATCAAGATATTTCTTTGCTGAAGTATTTAAATCTTATCC  
TTGTATCTTTTTATACATATTTGAAAATAAGCTTATATGTATTTGAACTTTTTTGAAATC  
CTATTCAAGTATTTTTATCATGCTATTGTGATATTTAGCACTTTGGTAGCTTTTACACT  
GAATTTCTAAGAAAATTGTAAAATAGTCTTCTTTTATACTGTAAAAAAGATATACCAA  
AAAGTCTTATAATAGGAATTTAACTTTAAAAACCCACTTATTGATACCTTACCATCTAA  
AATGTGTGATTTTTATAGTCTCGTTTTAGGAATTTACAGATCTAAATTATGTAAGTGA  
AATAAGGTGCTTACTCAAAGAGTGTCCACTATTGATTGTATTATGCTGCTCACTGATCC  
TTCTGCATATTTAAAATAAAATGTCCTAAAGGGTTAGTAGACAAAATGTTAGTCTTTTG  
TATATTAGGCCAAGTGCAATTGACTTCCCTTTTTTAATGTTTCATGACCACCCATTGATT  
GTATTATAACCACTTACAGTTGCTTATTTTTTGTTTTAACTTTTGTTCCTTAACATTTA  
GAATATTACATTTTGTATTATACAGTACCTTTCTCAGACATTTTGTAG

Figure 68

MEMFTFLLTCIFLPLLRGHSLFTCEPITVPRCMKMAYNMTFFPNLMGHYDQSIAAVEMEHF  
LPLANLECSPIETFLCKAFVPTCIEQIHVPPCRKLCEKVYSDCKKLIDTFGIRWPEELED  
RLQYCDETVPVTFDPHTEFLGPQKKTEQVQRDIGFWCPRHLKTSGGQGYKFLGIDQCAPP  
PNMYFKSDELEFAKSFIGHTVSIFCLCATLFTFLTLFIDVRRFRYPERPITYYSVCYSIVSLMYFI  
GFLLGDSTACNKADEKLELGDVTVLGSQNKACTVLFMLLYFFTMAGTVWWVILTITWFLA  
AGRKWSCEAIEQKAVWFHAVA WGTGFLTVMLLALNKVEGDNISGVCFVGLYDLDDASRY  
FVLLPLCLCVFVGLSLLLAGHSLNHVRQVIQHDGRNQEKLLKFMIRIGVFSGLYLVLVTL  
GCYVYEQVNRTWEITWVSDHCRQYHIPCPYQAKAKARPELALFMIKYLMTLIVGISA  
VFWVGSKKTCTEWAGFFKRNRKRDPISESRRVLQESCEFLKHNSKVHKHKKHYKPSSHK  
LKVISKSMGTSTGATANHGTSVAITSHDYLGQETLTEIQTSPETSMREVKADGASTPRLRE  
QDCGEPASPAASISRLSGEQVDGKGQAGSVSESARSEGRISPKSDITDTGLAQSNLQVPSS  
EPSSLKGSTSLLVHPVSGVRKEQGGGCHSDT

Figure 69

CTCTCCCAACCGCCTCGTCGCACTCCTCAGGCTGAGAGCACCGCTGCACTCGCGGCCGG  
CGATGCGGGACCCCGGCGCGGCCGCTCCGCTTTCTGTCCTGGGCTCTGTGCCCTGGTG  
CTGGCGCTGCTGGGCGCACTGTCCGCGGGCGCCGGGGCGCAGCCGTACCACGGAGAGA  
AGGGCATCTCCGTGCCGACACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACG  
GACATCGCCTACAACCAGACCATCCTGCCCAACCTGCTGGGCCACACGAACCAAGAGG  
ACGCGGGCCTCGAGGTGCACCAGTTCTACCCGCTGGTGAAGGTGCAGTGTCTCCGA  
ACTCCGCTTTTTCTTATGCTCCATGTATGCGCCCGTGTGCACCGTGCTCGATCAGGCCAT  
CCCGCCGTGTCGTTCTCTGTGCGAGCGCGCCCGCCAGGGCTGCGAGGCGCTCATGAAC  
AAGTTCGGCTTCCAGTGGCCCGAGCGGCTGCGCTGCGAGAACTTCCCGGTGCACGGTG  
CGGGCGAGATCTGCGTGGGCCAGAACACGTGCGACGGCTCCGGGGGCCCAGGCGGCG  
GCCCCACTGCCTACCCTACCGCGCCCTACCTGCCGGACCTGCCCTTACCGCGCTGCC

CAAGGTGCCCCCGTACCTGGGCTACCGCTTCTGGGTGAGCGCGATTGTGGCGCCCCGT  
GCCAACC GGCGCGTGCCAACGGCCTGATGTACTTTAAGGAGGAGGAGAGGGCGCTTCG  
CCGCCTCTGGGTGGGCGTGTGGTCCGTGCTGTGCTGCGCCTCGACGCTCTTTACCGTTC  
TCACCTACCTGGTGGACATGCGGGCGCTTCAGCTACCCAGAGCGGCCCATCATCTTCCTG  
TCGGGCTGCTACTTCATGGTGGCCGTGGCGCACGTGGCCGGCTTCCTTCTAGAGGACCG  
CGCCGTGTGCGTGGAGCGCTTCTCGGACGATGGCTACCGCACGGTGGCGCAGGGCACC  
AAGAAGGAGGGCTGCACCATCCTCTTCATGGTGGTCTACTTCTTCGGCATGGCCAGCTC  
CATCTGGTGGGTCAATTCTGTCTCTCACTTGGTTCCTGGCGGCCGGCATGAAGTGGGGCC  
ACGAGGCCATCGAGGCCAACTCGCAGTACTTCCACCTGGCCGCGTGGGCCGTGCCCGC  
CGTCAAGACCATCACTATCCTGGCCATGGGCCAGGTAGACGGGGACCTGCTGAGCGGG  
GTGTGCTACGTTGGCCTCTCCAGTGTGGACGCGCTGCGGGGCTTCGTGCTGGCGCCTCT  
GTTCTGTCTACCTCTTCATAGGCACGTCTTCTTGCTGGCCGGCTTCGTGTCCCTCTTCCG  
TATCCGCACCATCATGAAACACGACGGCACCAAGACCGAGAAGCTGGAGAAGCTCAT  
GGTGCGCATCGGCGTCTTCAGCGTGTCTACACAGTGCCCGCCACCATCGTCTTGGCCT  
GCTACTTCTACGAGCAGGCCTTCCGCGAGCACTGGGAGCGCACCTGGCTCCTGCAGAC  
GTGCAAGAGCTATGCCGTGCCCTGCCCGCCGGCCACTTCCCGCCCATGAGCCCCGACT  
TCACCGTCTTCATGATCAAGTACCTGATGACCATGATCGTCGGCATCACCACTGGCTTC  
TGGATCTGGTCGGGCAAGACCCTGCAGTCGTGGCGCCGCTTCTACCACAGACTTAGCC  
ACAGCAGCAAGGGGGAGACTGCGGTATGAGCCCCGGCCCCCTCCCCACCTTTCCACCC  
CAGCCCTCTTGCAAGAGGAGAGGCACGGTAGGGAAAAGAACTGCTGGGTGGGGGCCT  
GTTTCTGTAACTTTCTCCCCCTCTACTGAGAAGTGACCTGGAAGTGAGAAGTTCTTTC  
AGATTTGGGGCGAGGGGTGATTTGGAAAAGAACCTGGGTGGAAAGCGGTTTGAT  
GAAAAGATTTCAAGGCAAAGACTTGCAGGAAGATGATGATAACGGCGATGTGAATCGTC  
AAAGGTACGGGCCAGCTTGTGCCTAATAGAAGGTTGAGACCAGCAGAGACTGCTGTGA  
GTTTCTCCCGGCTCCGAGGCTGAACGGGGACTGTGAGCGATCCCCCTGCTGCAGGGCG  
AGTGGCCTGTCCAGACCCCTGTGAGGCCCGGGAAAGGTACAGCCCTGTCTGCGGTGG  
CTGCTTTGTTGGAAAGAGGGAGGGCCTCCTGCGGTGTGCTTGTCAAGCAGTGGTCAA  
CCATAATCTCTTTTCACTGGGGCCAACTGGAGCCCAGATGGGTAAATTTCCAGGGTCA  
GACATTACGGTCTCTCCTCCCCCTGCCCCCTCCCGCCTGTTTTCTCCCGTACTGCTTTC  
AGGTCTTGTAATAAAGCATTGGAAGTCTTGGGAGGCCTGCCTGCTAGAATCCTAATG  
TGAGGATGCAAAAGAAATGATGATAACATTTTGAGATAAGGCCAAGGAGACGTGGAG  
TAGGTATTTTTGCTACTTTTTCATTTTTCTGGGGAAGGCAGGAGGCAGAAAGACGGGTGT  
TTTATTTGGTCTAATACCCTGAAAAGAGTGATGACTTGTGCTTTTCAAAACAGGAAT  
GCATTTTTCCCTTGTCTTTGTTGTAAGAGACAAAAGAGGAAACAAAAGTGTCTCCCTG  
TGGAAGGCATAACTGTGACGAAAGCAACTTTTATAGGCAAAGCAGCGCAAATCTGAG  
GTTTCCCGTTGGTTGTTAATTTGGTTGAGATAAACATTCCTTTTTAAGGAAAAGTGAAG  
AGCAGTGTGCTGTACACACCCGTTAAGCCAGAGGTTCTGACTTCGCTAAAGGAAATGT  
AAGAGGTTTTGTTGTCTGTTTTAAATAAATTTAATTCGGAACACATGATCCAACAGACT  
ATGTTAAATATTCAAGGAAATCTCTCCCTTCACTTTTCTTGTCTATAAGCCTATA  
TTTAGGTTTCTTTTCTATTTTTTCTCCCATTTGGATCCTTTGAGGTAAAAAACATAAT  
GTCTTCAGCCTCATAATAAGGAAAGTTAATTAAGGAAAGGAAAGGAAAGGAAAGGAAAGG  
GTCTGTGTTTCTTGGTTCCATCAATCTGTTTATTAAACATCATCCATATGCTGACCCTGT  
CTCTGTGTTGTTGGGTTGGGAGGCGATCAGCAGATAACCATAGTGAACGAAGAGGAAGG  
TTTGAACCATGGGCCCCATCTTTAAAGAAAGTCATTAAAGAAAGGTAAGTCAAAAGT  
GATTCTGGAGTTCTTTGAAATGTGCTGGAAGACTTAAATTTATTAATCTTAAATCATGT  
ACTTTTTTCTGTAATAGAACTCGGATTCTTTTGCATGATGGGGTAAAGCTTAGCAGAG  
AATCATGGGAGCTAACCTTTATCCCACCTTTGACACTACCTCCAATCTTGCAACACTA  
TCCTGTTTCTCAGAACAGTTTTTAAATGCCAATCATAGAGGGTACTGTAAAGTGTACAA  
GTTACTTTATATATGTAATGTTCACTTGAGTGGAAGTCTTTTTACATTAAAGTTAAAT  
CGATCTTGTGTTTCTTCAACCTTCAAACTATCTCATCTGTGAGATTTTTTAAACTCCAA  
CACAGGTTTTGGCATCTTTTGTGCTGTATCTTTAAGTGCATGTGAAATTTGTAAATAG

TATTTATACATTTTACTTTGGATTTTGTGTTTGGCTTTAAAGGTCTACCCCACTTTA  
TCACATGTACAGATCACAAATAAATTTTTTAAATAC

Figure 70

MRDPGAAAPLSSLGLCALVLALLGALSAGAGAQPYHGEKGISVPDHGFCQPISIPLCDIAY  
NQILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFLLCSMYAPVCTVLDQAIPPCRSILC  
ERARQGCEALMNKFGFQWPERLRNENFVHGAGEICVQNTSDGSGGPGGGPTAYPTAPY  
LPDLPFTALPPGASDGRGRPAFPFSCPRQLKVPYPYLYRFLGERDCGAPCEPGRANGLMYF  
KEEERRFARLWVGWVSVLCCASTLFTVLTYLVDMMRFSYPERPIIFLSGCYFMVAVAHVA  
GFLI.EDRAVCVERFSDDGYRTVAQGTKKEGCTILFMVLYFFGMASSIWWVLSLTWFLAA  
GMKWGHEAIEANSQYFHLAAWAVPAVKTTITLAMGQVDGDLISGVCYVGLSSVDA  
LRGFVLAPLFVYLFITGSFLLAGFVSLFRITIMKHDGTEKLEKLMVRIGVFSVLYTVPAT  
IVLACYFYEQAFREHWERTWLLQTKSYAVPCPPGHFPPMSPDFTVFMKYLMTMIVGITT  
GFWIWSGKTLQSWRRFYHRLSHSSKGETAV

Figure71

ACAGCATGGAGTGGGGTTACCTGTTGGAAGTGACCTCGCTGCTGGCCGCCTTGGCGCT  
GCTGCAGCGCTCTAGCGGCGCTGCGGCCGCTCGGCCAAGGAGCTGGCATGCCAAGAG  
ATCACCGTGCCGCTGTGTAAGGGCATCGGCTACAACCTACACCTACATGCCCAATCAGTT  
CAACCACGACACGCAAGACGAGGCGGGCCTGGAGGTGCACCAGTTCTGGCCGCTGGTG  
GAGATCCAGTGCTCGCCGATCTCAAGTTCTTCTGTGCAGCATGTACACGCCCATCTG  
CCTAGAGGACTACAAGAAGCCGCTGCCGCCCTGCCGCTCGGTGTGCGAGCGCGCCAAG  
GCCGGCTGCGCGCCGCTCATGCGCCAGTACGGCTTCGCTGGCCCGACCGCATGCGCT  
GCGACCGGCTGCCCGAGCAAGGCAACCCTGACACGCTGTGCATGGACTACAACCGCAC  
CGACCTAACCACCGCCGCGCCAGCCCGCCGCGCCGCTGCCGCGCCGCGCCGCGCCGCG  
GAGCAGCCGCTTCGGGCAGCGGCCACGGCCGCGCCGCGGGGGCCAGGCCCCCGCACC  
GCGGAGGCGGCAGGGGCGGTGGCGGCGGGGACGCGGCGGCGCCCCAGCTCGCGGGCG  
GCGGCGGTGGCGGGAAGGCGCGGCCCCCTGGCGGCGGCGCGGCTCCCTGCGAGCCCCG  
GGTGCCAGTGCCGCGCGCCTATGGTGAGCGTGTCCAGCGAGCGCCACCCGCTCTACAA  
CCGCGTCAAGACAGGCCAGATCGCTAACTGCGCGCTGCCCTGCCACAACCCCTTTTCA  
GCCAGGACGAGCGCGCCTTACCGTCTTCTGGATCGGCCTGTGGTGGTGCTCTGCTTC  
GTGTCCACCTTCGCCACCGTCTCCACCTTCTTATCGACATGGAGCGCTTCAAGTACCC  
GGAGCGGCCCAATTATCTTCTCTCGGCCTGCTACCTCTTCGTGTGGTGGGCTACCTAG  
TGCGCCTGTTGGCGGGCCACGAGAAGGTGGCGTGCAGCGGTGGCGCGCCGGGCGCGG  
GGGGCGCTGGGGGCGCGGGCGGCGGCGGGCGGGCGGGCGGGCGGGCGGGCGGGCGG  
CGGGCGGCCCGGGCGGGCGGCGGAGTACGAGGAGCTGGGCGCGGTGGAGCAGCACG  
TGCGCTACGAGACCACCGGCCCGCGCTGTGCACCGTGGTCTTCTTGCTGGTCTACTTC  
TTCGGCATGGCCAGCTCCATCTGGTGGGTGATCTTGTGCTCACATGGTTCCTGGCGGC  
CGGTATGAAGTGGGGCAACGAAGCCATCGCCGGCTACTCGCAGTACTTCCACCTGGCC  
GCGTGGCTTGTGCCAGCGTCAAGTCCATCGCGGTGCTGGCGCTCAGCTCGGTGGACG  
GCGACCCGGTGGCGGGCATCTGCTACGTGGGCAACCAGAGCCTGGACAACCTGCGCGG  
CTTCGTGCTGGCGCCGCTGGTCATCTACCTCTTCATCGGCACCATGTTCTGCTGGCCG  
GCTTCGTGTCCTGTTCCGCATCCGCTCGGTTCATCAAGCAACAGGACGGCCCCACCAAG  
ACGCACAAGCTGGAGAAGCTGATGATCCGCCTGGGCCTGTTACCGTGCTCTACACCG  
TGCCCGCCGCGGTGGTGGTGCCTGCTTCTACGAGCAGCACAACCGCCCGCGCTG  
GGAGGCCACGCACAACCTGCCCGTGCCTGCGGGACCTGCAGCCCGACCAAGCACGAG  
GCCCCGACTACGCCGTCTTCATGCTCAAGTACTTCATGTGCCTAGTGGTGGGCATCACCT  
CGGGCGTGTGGGTCTGGTCCGGCAAGACGCTGGAGTCCTGGCGCTCCCTGTGCACCCG  
CTGCTGCTGGGCCAGCAAGGGCGCCGCGGTGGGCGGGGGCGCGGGCGCCACGGCCGCG

GGCCGGGCGGGCGGGCGGGGGCTCCCTCTACAGCGACGTCAGCACTGGCCTGACGTGGCG  
GTCGGGCACGGCGAGCTCCGTGTCTTATCCAAAGCAGATGCCATTGTCCCAGGTCTGA  
GCGGAGGGGAGGGGGCGCCAGGAGGGGTGGGGAGGGGGGCGAGGAGACCCAAGTG  
CAGCGAAGGGACACTTGATGGGCTGAGGTTCCACCCCTTCACAGTGTTGATTGCTATT  
AGCATGATAATGAACTCTTAATGGTATCCATTAGCTGGGACTTAAATGACTCACTAGA  
ACAAAGTACCTGGCATTGAAGCCTCCCAGACCCAGCCCCTTTCTCCTCATTGATGTGCG  
GGGAGCTCCTCCCGCCACGCGTTAATTTCTGTTGGCTGAGGAGGGGTGGACTCTGCGGCG  
TTCCAGAACCCGAGATTTGGAGCCCTCCCTGGCTGCACTTGGCTGGGTTTGCAGTCAG  
ATACACAGATTTACCTGGGAGAACCTCTTTTTCTCCCTCGACTCTTCCTACGTAAACTC  
CCACCCCTGACTTACCCTGGAGGAGGGGTGACCGCCACCTGATGGGATTGCACGGTTT  
GGGTATTCTTAATGACCAGGCAAATGCCTTAAGTAAACAAACAAGAAATGTCTTAATT  
ATACACCCACGTAAATACGGGTTTCTTACATTAGAGGATGTATTTATATAATTATTTG  
TTAAATTGTAAAAAAGTGTAAAATATGTATATATCCAAAGATATAGTGTGTAC  
ATTTTTTTGTAAAAAGTTTAGAGGCTTACCCCTGTAAGAACAGATATAAGTATTCTATT  
TTGTCAATAAAATGACTTTTGATAAATGATTAAACCATTGCCCTCTCCCCCGCCTCTTCT  
GAGCTGTCACCTTTAAAGTGCTTGCTAAGGACGCATGGGGAAAATGGACATTTTCTGG  
CTTGTCATTCTGTACACTGACCTTAGGCATGGAGAAAATTACTTGTTAAACTCTAGTTC  
TTAAGTTGTTAGCCAAGTAAATATCATTGTTGAACTGAAATCAAATTGAGTTTTTGCA  
CCTTCCCCAAAGACGGTGTTTTTCATGGGAGCTCTTTTCTGATCCATGGATAACAACCTC  
TCACTTTAGTGGATGTAAATGGAACCTCTGCAAGGCAGTAATCCCCTTAGGCCTTGTT  
ATTTATCCTGCATGGTATCACTAAAGGTTTCAAAACCCTGAAAAAAA

Figure 72

MEWGYLLEVTSLAALALLQRSSGAAAASAKELACQEITVPLCKGIGYNYTYMPNQFNHD  
TQDEAGLEVHQFWPLVEIQSPDLKFFLCMYTPICLEDYKKPLPPCRSVCERAKAGCAPL  
MRQYGFAWPDRMRCDRLPEQGNPD TLCMDYNRTDLTTAAPSPPRRLPPPPPGEQPPSGS  
HGRPPGARPPHRGGGRGGGGGDAAPPARGGGGGGKARPPGGGAAPCEPGCQCRAPMVS  
VSSERHPLYNRVKTGOIANCALPCHNPFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLID  
MERFKYPERPIIFLSACYLFVSVGYLVRLVAGHEKVACSGGAPGAGGAGGAGGAAAGAG  
AAGAGAGGPGGRGEYEELGAVEQHVRYETTPALCTVVFLLVYFFGMASSIWWVILSLT  
WFLAAGMKWGNELIAGYSQYFHLAAWLVPVSKIAVLALSSVDGDPVAGICYVGNQSLD  
NLRGFVLAPLVIYLFITMFLLAGFVSLFRIRSVIKQQDGPTKTHKLEKLMIRLGLFTVLYTV  
PAAVVVACLFYEQHNRPRWEATHNCPCLRDLPDQARRPDYAVFMLKYFMCLVVGITSG  
VWVWSGKTLWSRSLCTRCCWASKGAAVGGGAGATAAGGGGGGPGGGGGGGPGGGGGP  
GGGGGSLYSDVSTGLTWRS GTASSVSYPKQMPLSQV

Figure 73

CCGCCTTCGGCCCGGGCCTCCCGGGATGGCCGTGGCGCCTCTGCGGGGGGGCGCTGCTG  
CTGTGGCAGCTGCTGGCGGCGGGCGGCGCGGCACTGGAGATCGGCCGCTTCGACCCGG  
AGCGCGGGCGCGGGGCTGCGCCGTGCCAGGCGGTGGAGATCCCCATGTGCCGCGGCAT  
CGGCTACAACCTGACCCGCATGCCAACCTGCTGGGCCACACGTCGCAGGGCGAGGCG  
GCTGCCGAGCTAGCGGAGTTGCGCGCCGTGGTGCAGTACGGCTGCCACAGCCACCTGC  
GCTTCTTCCTGTGCTCGCTCTACGCGCCCATGTGCACCGACCAGGTCTCGACGCCCAT  
CCCGCCTGCCGGCCCATGTGCGAGCAGGCGCGCCTGCGCTGCGCGCCCATCATGGAGC  
AGTTCAACTTCGGCTGGCCGGACTCGCTCGACTGCGCCCGGCTGCCACGCGCAACGA  
CCCGCACGCGCTGTGCATGGAGGCGCCCGAGAACGCCACGGCCGGCCCCGCGGAGCCC



TGGGCCCCGGGCGCGGGCGGCAGTGGCACCTGCGAGAACCCCGAGAAGTTCCAGTACGT  
GGAGAAGAGCCGCTCGTGCGCACCGCGCTGCGGGCCCGGCGTCGAGGTGTTCTGGTCC  
CGGCGCGACAAGGACTTCGCGCTGGTCTGGATGGCCGTGTGGTCGGCGCTGTGCTTCTT  
CTCCACCGCCTTCACTGTGCTCACCTTCTTGCTGGAGCCCCACCGCTTCCAGTACCCCG  
AGCGCCCCATCATCTTCTCTCCATGTGCTACAACGTCTACTCGCTGGCCTTCTGATCC  
GTGCGGTGGCCGGAGCGCAGAGCGTGGCCTGTGACCAGGAGGCGGGCGCGCTCTACGT  
GATCCAGGAGGGCCTGGAGAACACGGGCTGCACGCTGGTCTTCTACTGCTCTACTAC  
TTCGGCATGGCCAGCTCGCTCTGGTGGGTGGTCTGACGCTCACCTGGTTCCTGGCTGC  
CGGAAGAAATGGGGCCACGAGGCCATCGAGGCCACGGCAGCTATTTCCACATGGCT  
GCCTGGGGCCTGCCC GCGCTCAAGACCATCGTCATCCTGACCCTGCGCAAGGTGGCGG  
GTGATGAGCTGACTGGGCTTTGCTACGTGGCCAGCACGGATGCAGCAGCGCTCACGGG  
CTTCGTGCTGGTGCCCTCTCTGGCTACCTGGTGCTGGGCAGTAGTTTCTCTGACCG  
GCTTCGTGGCCCTCTTCCACATCCGCAAGATCATGAAGACGGGCGGCACCAACACAGA  
GAAGCTGGAGAAGCTCATGGTCAAGATCGGGGTCTTCTCCATCCTCTACACGGTGCCC  
GCCACCTGCGTCATCGTTTGCTATGTCTACGAACGCCTCAACATGGACTTCTGGCGCCT  
TCGGGCCACAGAGCAGCCATGCGCAGCGGCCGCGGGGCCCGGAGGCCGGAGGGACTG  
CTCGCTGCCAGGGGGCTCGGTGCCACCGTGGCGGTCTTCATGCTCAAAATTTTCATGT  
CACTGGTGGTGGGGATCACCGAGCGGCGTCTGGGTGTGGAGCTCCAAGACTTTCCAGAC  
CTGGCAGAGCCTGTGCTACCGCAAGATAGCAGCTGGCCGGGCCCGGCCAAGGCCTGC  
CGCGCCCCCGGGAGCTACGGACGTGGCACGCACTGCCACTATAAGGCTCCCACCGTGG  
TCTTGCACATGACTAAGACGGACCCCTCTTTGGAGAACCCACACACCTCTAGCCACAC  
AGGCCTGGCGCGGGGTGGCTGCTGCCCCCTCCTTGCCCTCCACGCCCTGCCCCCTGCAT  
CCCCTAGAGACAGCTGACTAGCAGCTGCCAGCTGTCAAGGTCAGGCAAGTGAGCACC  
GGGGACTGAGGATCAGGGCGGGACCCCGTGAGGCTCATTAGGGGAGATGGGGGTCTC  
CCCTAATGCGGGGGCTGGACCAGGCTGAGTCCCCACAGGGTCTAGTGGAGGATGTGG  
AGGGGCGGGGCAGAGGGGTCCAGCCGAGTTTATTTAATGATGTAATTTATTGTGCG  
TTCCTCTGGAAGCTGTGACTGGAATAAACCCCGCGTGGCACTGCTGATCCTCTCTGGC  
TGGGAAGGGGGAAGGTAGGAGGTGAGGC

Figure 74

MAVAPLRGALLLWQLLAAGGALEIGRFDPERGRGAAPCQAVEIPMCRGIGYNLTRMPNL  
LGHTSQGEAAAELAEFAPLVQYGCHSHLRFFLCSLYAPMCTDQVSTPIPACRPMCEQARLR  
CAPIMEQFNFGWPDSDLCARLPTRNDPHALCMEAPENATAGPAEPHKGLGMLPVAPRPAR  
PPGDLPGAGGSGTCENPEKFQYVEKSRSCAPRCGPVEVFWSSRRDKDFALVWMAVWSA  
LCFFSTAFTVLTFLLPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAGAQSACDQAEAGALY  
VIEGLENTGCTLVFLLLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMA  
AWGLPALKTIVILTLRKVAGDELTGLCYVASTDAAALTGFVLVPLSGYLVLGSSFLLTG  
FVALFHIRKIMKTGGTNTKLEKLMVKIGVFSILYTPATCVIVCYVYERLNMDFWRLRAT  
EQPCAAAAGPGGRRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSSKTFQTWQSLC  
YRKIAAGRARAKACRAPGSYGRGTHCHYKAPTIVLHMTKTDPSLENPHL

Figure 75

ACACGTCCAACGCCAGCATGCAGCGCCCCGGGCCCCCGCCTGTGGCTGGTCTGCAGGT  
GATGGGCTCGTGCGCCGCCATCAGCTCCATGGACATGGAGCGCCCGGGCGACGGCAAA  
TGCCAGCCCATCGAGATCCCGATGTGCAAGGACATCGGCTACAACATGACTCGTATGC  
CCAACCTGATGGGCCACGAGAACCAGCGCGAGGCAGCCATCCAGTTGCACGAGTTTCG  
GCCGCTGGTGGAGTACGGCTGCCACGGCCACCTCCGCTTCTTCTGTGCTCGCTGTACG  
CGCCGATGTGCACCGAGCAGGTCTCTACCCCATCCCCGCTGCCGGGTGATGTGCGA  
CGACCGCGCGCTCACTGCTCCCGATTATGGAGCAGTTCAACTTCAAGTGGCCCGAC

TCCCTGGACTGCCGGAACTCCCCAACAAGAACGACCCCAACTACCTGTGCATGGAGG  
CGCCCAACAACGGGCTCGGACGAGCCCACCCGGGGCTCGGGCCTGTTCCCGCCGCTGTT  
CCGGCCGCAGCGGCCCCACAGCGCGCAGGAGCACCCGCTGAAGGACGGGGGCCCCGG  
GCGCGGCGGCTGCGACAACCCGGGCAAGTTCCACCACGTGGAGAAGAGCGCGTCTG  
CGCGCCGCTCTGCACGCCCCGGCGTGGACGTGTACTGGAGCCGCGAGGACAAGCGCTT  
GCAGTGGTCTGGCTGGCCATCTGGGCGGTGCTGTGCTTCTTCTCCAGCGCCTTACCGT  
GCTCACCTTCCTCATCGACCCGGCCCGCTTCCGCTACCCGAGCGCCCCATCATCTTCC  
TCTCCATGTGCTACTGCGTCTACTCCGTGGGCTACCTCATCCGCCTCTTCGCCGGCGCC  
GAGAGCATCGCCTGCGACCCGGGACAGCGGCCAGCTCTATGTCATCCAGGAGGGACTGG  
AGAGCACCGGCTGCACGCTGGTCTTCTTGGTCTCTACTACTTCGGCATGGCCAGCTCG  
CTGTGGTGGGTGGTCTCACGCTCACCTGGTTCCTGGCCGCCGCAAGAAGTGGGGCC  
ACGAGGCCATCGAAGCCAACAGCAGCTACTTCCACCTGGCAGCCTGGGCCATCCCCGGC  
GGTGAAGACCATCCTGATCCTGGTCATGCGCAGGGTGGCGGGGGACGAGCTCACCGGG  
GTCTGCTACGTGGGCAGCATGGACGTCAACGCGCTCACCGGCTTCGTGCTCATTCCCCT  
GGCCTGCTACCTGGTCATCGGCACGTCTTTCATCCTCTCGGGCTTCGTGGCCCTGTTCC  
ACATCCGGAGGGTGTGAAGACGGGCGGCGAGAACACGGACAAGCTGGAGAAGCTCA  
TGGTGCATATCGGGCTCTTCTCTGTGCTGTACACCGTGCCGGCCACCTGTGTGATCGCC  
TGCTACTTTTACGAACGCCTCAACATGGATTACTGGAAGATCCTGGCGGCGCAGCACA  
AGTGCAAAATGAACAACCAAGACTAAAACGCTGGACTGCCTGATGGCCGCCTCCATCCC  
CGCCGTGGAGATCTTCATGGTGAAGATCTTTATGCTGCTGGTGGTGGGGATCACCAGCG  
GGATGTGGATTTGGACCTCCAAGACTCTGCAGTCCTGGCAGCAGGTGTGCAGCCGTAG  
GTTAAAGAAGAAGAGCCGGAGAAAACCGGCCAGCGTGATCACCAGCGGTGGGATTTA  
CAAAAAAGCCCAGCATCCCCAGAAAACCTACCCAGGGGAAATATGAGATCCCTGCCAG  
TCGCCACCTGCGTGTGAACAGGGCTGGAGGGAAGGGCACAGGGGCGCCCGGAGCTA  
AGATGTGGTGCTTTTTCTTGGTTGTGTTTTTCTTTCTTCTTCTTTTTTTTTTATAA  
AAGCAAAAGAGAAATACATAAAAAAGTGTTTACCCTGAAATTCAGGATGCTGTGATAC  
ACTGAAAGGAAAAATGTACTTAAAGGGTTTTGTTTTGTTTTGGTTTTCCAGCGAAGGGA  
AGCTCCTCCAGTGAAGTAGCCTCTTGTGTAATAATTTGTGGTAAAGTAGTTGATTGAG  
CCCTCAGAAGAAAACCTTTGTTTAGAGCCCTCCGTAAATATACATCTGTGTATTGAGT  
TGGCTTTGCTACCCATTTACAAATAAGAGGACAGATAACTGCTTTGCAAATTCAGAGC  
CTCCCTGGGTAAACAAATGAGCCATCCCCAGGGCCACCCCCAGGAAGGCCACAGTG  
CTGGGCGGCATCCCTGCAGAGGAAAGACAGGACCCGGGGCCCGCCTCACACCCAGTG  
GATTTGGAGTTGCTTAAAATAGACTCTGGCCTTACCAATAGTCTCTCTGCAAGACAGA  
AACCTCCATCAAACCTCACATTTGTGAACCTCAAACGATGTGCAATACATTTTTTCTCTT  
TCCTTGAAAATAAAAAGAGAAACAAGTATTTTGCTATATATAAAGACAACAAAAGAAA  
TCTCCTAACAAAAGAACTAAGAGGCCAGCCCTCAGAAACCTTCAGTGCTACATTTT  
GTGGCTTTTTAATGGAAACCAAGCCAATGTTATAGACGTTTGGACTGATTTGTGGAAAG  
GAGGGGGGAAGAGGGGAGAAGGATCATTCAAAGTTACCCAAAGGGCTTATTGACTCTT  
TCTATTGTAAACAAATGATTTCCACAAACAGATCAGGAAGCACTAGGTGGCAGAGA  
CACTTTGTCTAGTGTATTCTCTTCACAGTGCCAGGAAAGAGTGGTTTCTGCGTGTGTAT  
ATTTGTAATATATGATATTTTTCATGCTCCACTATTTTATTAAAAATAAAATATGTTCTT  
TAAAAAAA

Figure 76

MQRPGPRLWLVLQVMGSCAAISSMDMERPGDGKQCPIEIPMCKDIGYNMTRMPNLMGHE  
NQREAAIQLHEFAPLVEYGCHGHLRFFLCSLYAPMCTEQVSTPIPACRVMCEQARLKCSPI  
MEQFNFKWPDSDLCKLPNKNDPNYLCMEAPNNGSDEPTRGSLFPPLFRPQRPHSAQEH  
PLKDGGPGRGGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDKRFVWVLAJWAVLFCF  
FSSAFTVLTFLIDPARFRYPERPIIFLSMCYCVYSVGYLRLFAGAESIACDRDSGQLYVIEG  
LESTGCTLVFLVLYYFGMASSLWVVLTLTWFLAAGKKWGHEAIEANSSYFHLAAWAIP  
AATTTTITVMPRVAGDRI TGVCYVVGSMVNAITGFEVIPIACYLVIIGTSFILSGFVAL



FHIRRVMKTGGENTDKLEKLMVRIGLFSVLYTVPATCVIACYFYERLNMDYWKILAAQHK  
CKMNNQTKTLDCDMAASIPAVEIFMVKIFMLLVVGITSGMWIWTSTLQSWQQVCSRRLK  
KKSRRKPASVITSGGIYKKAQHPQKTHHGKYBPAQSPTCV

Figure 77

CCTGCAGCCTCCGGAGTCAGTGCCGCGCGCCCGCCGCCCCGCGCCTTCCTGCTCGCCGC  
ACCTCCGGGAGCCGGGGCGCACCCAGCCCGCAGCGCCGCTCCCCGCCGCGCCGCT  
CCGACCGCAGGCCGAGGGCCGCCACTGGCCGGGGGGACCGGGCAGCAGCTTGCGGCC  
GCGGAGCCGGGCAACGCTGGGGACTGCGCCTTTTGTCCCCGGAGGTCCCTGGAAGTTT  
GCGGCAGGACGCGCGCGGGGAGGCGGCGGAGGCAGCCCCGACGTGCGGAGAACAGG  
GCGCAGAGCCGGCATGGGCATCGGGCGCAGCGAGGGGGGCCGCCGCGGGGCCCTGGG  
CGTGCTGCTGGCGCTGGGCGCGGCGCTTCTGGCCGTGGGCTCGGCCAGCGAGTACGAC  
TACGTGAGCTTCCAGTCGGACATCGGCCCCGTACCAGAGCGGGCGCTTCTACACCAAGC  
CACCTCAGTGCGTGGACATCCCCGCGGACCTGCGGCTGTGCCACAACGTGGGCTACAA  
GAAGATGGTGCTGCCAACCTGCTGGAGCACGAGACCATGGCGGAGGTGAAGCAGCA  
GGCCAGCAGCTGGGTGCCCCCTGCTCAACAAGAACTGCCACGCCGGGACCCAGGTCTTC  
CTCTGCTCGCTCTTCGCGCCCGTCTGCCTGGACCGGCCCATCTACCCGTGTCGCTGGCT  
CTGCGAGGCCGTGCGCGACTCGTGCGAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGC  
CCGAGATGCTTAAGTGTGACAAGTTCCCGGAGGGGGACGTCTGCATCGCCATGACGCC  
GCCCAATGCCACCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCTCCCTGTGAC  
AACGAGTTGAAATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGCAGTGA  
GGATGAAAATAAAAGAAGTGAAAAAAGAAAATGGCGACAAGAAGATTGTCCCCAAGA  
AGAAGAAGCCCCTGAAGTTGGGGCCCATCAAGAAGAAGGACCTGAAGAAGCTTGTGC  
TGTACCTGAAGAATGGGGCTGACTGTCCCTGCCACCAGCTGGACAACCTCAGCCACCA  
CTTCCTCATCATGGGGCCGCAAGGTGAAGAGCCAGTACTTGCTGACGGCCATCCACAAG  
TGGGACAAGAAAAACAAGGAGTTCAAAAACCTTCATGAAGAAAATGAAAAACCATGAG  
TGCCCCACCTTTCAGTCCGTGTTTAAGTGATTCTCCCGGGGGCAGGGTGGGGAGGGAG  
CCTCGGGTGGGGTGGGAGCGGGGGGGACAGTGCCCGGGAACCCGTGGTCACACACAC  
GCACTGCCCTGTGAGTAGTGACATTGTAATCCAGTCGGCTTGTCTTGCAGCATTCCT  
GCTCCCTTTCCCTCCATAGCCACGCTCCAAACCCAGGGTAGCCATGGCCGGGTAAAG  
CAAGGGCCATTTAGATTAGGAAGGTTTTTAAGATCCGCAATGTGGAGCAGCAGCCACT  
GCACAGGAGGAGGTGACAAACCATTTCACACAGCAACACAGCCACTAAAACACAAAA  
AGGGGGATTGGGCGGAAAGTGAGAGCCAGCAGCAAAAACCTACATTTTGCAACTTGTTG  
GTGTGGATCTATTGGCTGATCTATGCCTTTCACTAGAAAATTCTAATGATTGGCAAGT  
CACGTTGTTTTCAGGTCCAGAGTAGTTTCTTTCTGTCTGCTTTAAATGGAAACAGACTC  
ATACCACACTTACAATTAAGGTCAAGCCAGAAAGTGATAAGTGACGGGAGGAAAAG  
TGCAAGTCCATTATCTAATAGTGACAGCAAAGGGACCAGGGGAGAGGCATTGCCTTCT  
CTGCCACAGTCTTTCCGTGTGATTGTCTTTGAATCTGAATCAGCCAGTCTCAGATGCC  
CCAAAGTTTCGGTTCCTATGAGCCCGGGGCATGATCTGATCCCCAAGACATGTGGAGG  
GGCAGCCTGTGCCTGCCTTTGTGTGAGAAAAAGGAAACACAGTGAGCCTGAGAGAGA  
CGGCGATTTTCGGGCTGAGAAGGCAGTAGTTTTCAAAACACATAGTTA

Figure 78

MGIGRSEGGRRGAALGVLLALGAALLAVGSASEYDYVSFQSDIGPYQSGRFYTKPPQCVDI  
PADLRLCHNVGYKKMVLNLEHETMAEVKQOASSWVPLLKNKNCHAGTQVFLCSLFAPV  
CLDRPIYPCRWLCEAVRDSCEPVMQFFGFYWP EMLKCDKFPEGDVCIAMTPPNATEASKP  
QGTTVCPPCDNELKSEAIEHLCASEFGLSLKMIVGSSHNSCCTLGPSHPNSSKRQEQLGTP  
PPDLGVCVLLHETQENTPPPCAQARSRMRIKTRATPLALGRSAPGLFADCPERPLPVCSFPH

Figure 79

Figure 80

Figure 81

CCGGGTCGGAGCCCCCGGAGCTGCGCGCGGGCTTGCAGCGCCTCGCCCGCGCTGTCC  
TCCCGGTGTCCCGCTTCTCCGCGCCCCAGCCGCGGGCTGCCAGCTTTTCGGGGCCCCGA  
GTCGCACCCAGCGAAGAGAGCGGGGCCCGGACAAAGCTCGAACTCCGGCCGCCTCGCCC  
TTCCCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTGCGCGCGCCACGATGCTGCAGGGCC  
CTGGCTCGCTGCTGCTGCTCTTCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGG  
CTCTTCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATC  
CCTGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGGCTGCCCAACC  
TGCTGGGCCACGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCT  
GGTCATGAAGCAGTGCCACCCGGACACCAAGAAGTTCTGTGCTCGCTCTTCGCCCCC  
GTCTGCCTCGATGACCTAGACGAGACCATCCAGCCATGCCACTCGCTCTGCGTGCAGGT  
GAAGGACCGCTGCGCCCCGGTCATGTCCGCCTTCGGCTTCCCCTGGCCCGACATGCTTG  
AGTGCGACCGTTTCCCCCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCA  
CCTCCTGCCAGCCACCGAGGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAAAT  
GATGATGACAACGACATAATGGAAACGCTTTGTAAAAATGATTTTGCCTGAAATAA  
GATGATGACAACGACATAATGGAAACGCTTTGTAAAAATGATTTTGCCTGAAATAA

GCAAGACCATTTACAAGCTGAACGGTGTGTCCGAAAGGGACCTGAAGAAATCGGTGCT  
GTGGCTCAAAGACAGCTTGCAGTGCACCTGTGAGGAGATGAACGACATCAACGCGCCC  
TATCTGGTCATGGGACAGAAACAGGGTGGGGAGCTGGTGATCACCTCGGTGAAGCGGT  
GGCAGAAGGGGCAGAGAGAGTTCAAGCGCATCTCCCGCAGCATCCGCAAGCTGCAGT  
GCTAGTCCCGGCATCCTGATGGCTCCGACAGGCCTGCTCCAGAGCACGGCTGACCATT  
CTGCTCCGGGATCTCAGCTCCCGTTCCCCAAGCACACTCCTAGCTGCTCCAGTCTCAGC  
CTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCATCCCCAGCATTTCCTGAGTTATAAG  
GCCACAGGAGTGGATAGCTGTTTTACCTAAAGGAAAAGCCCACCCGA  
ATCTTGTAAGAAATATTCAAATAATAAATCATGAATATTTTATGAAGTTT

Figure 82

MLQPGSLLLLFLASHCCLGSARGLFLFGQPDFSYKRSNCKPIPANLQLCHGIEYQNMRLP  
NLLGHETMKEVLEQAGAWIPLVMKQCHPDTKKFLCSLFAPVCLDDLDETIQPCHSCLVQV  
KDRCAPVMSAFGFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEAPKVCEACKNKND  
DNDIMETLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLVNSERDLKKSVLWLKDSL  
QCTCEEMNDINAPYLVMGQKQGGELVITSVKRWQKGQREFKRISRSIRKLQC

Figure 83

ACGGGGCCTGGGCGGSAGGGGCGGTGGCTGGAGCTCGGTAAAGCTCGTGGGACCCCAT  
TGGGGGAATTTGATCCAAGGAAGCGGTGATTGCCGGGGGAGGAGAAGCTCCCAGATCC  
TTGTGTCCACTTGCAGCGGGGAGGCGGAGACGCGGAGCGGGCCTTTTGGCGTCCACT  
GCGCGGCTGCACCCTGCCCCATCCTGCCGGGATCATGGTCTGCGGCAGCCCGGGAGGG  
ATGCTGCTGCTGCGGGCCGGGCTGCTTGCCCTGGCTGCTCTCTGCCTGCTCCGGGTGCC  
CGGGGCTCGGGCTGCAGCCTGTGAGCCCGTCCGCATCCCCCTGTGCAAGTCCCTGCCCT  
GGAACATGACTAAGATGCCCAACCACCTGCACCACAGCACTCAGGCCAACGCCATCCT  
GGCCATCGAGCAGTTCGAAGGTCTGCTGGGCACCCACTGCAGCCCCGATCTGCTCTTCT  
TCCTCTGTGCCATGTACGCGCCCATCTGCACCATTGACTTCCAGCACGAGCCCATCAAC  
CCCTGTAAGTCTGTGTGCGAGCGGGCCCGGCAGGGCTGTGAGCCCATACTCATCAAGT  
ACCGCCACTCGTGGCCGGAGAACCTGGCCTGCGAGGAGCTGCCAGTGTACGACAGGGG  
CGTGTGCATCTCTCCCGAGGCCATCGTTACTGCGGACGGAGCTGATTTTCTATGGATT  
CTAGTAACGGAACTGTAGAGGGGCAAGCAGTGAACGCTGTAAATGTAAGCCTATTAG  
AGCTACACAGAAGACCTATTTCCGGAACAATTACAATATGTCATTGGGGCTAAAGTT  
AAAGAGATAAAGACTAAGTGCCATGATGTGACTGCAGTAGTGAGGTGAAGGAGATT  
CTAAAGTCCTCTCTGGTAAACATTCCACGGGACACTGTCAACCTCTATAACCAGCTCTGG  
CTGCCTCTGCCCTCCACTTAATGTAAATGAGGAATATATCATCATGGGCTATGAAGATG  
AGGAACGTTCCAGATTACTCTTGGTGGAAGGCTCTATAGCTGAGAAGTGGAAGGATCG  
ACTCGGTAAAAAAGTTAAGCGCTGGGATATGAAGCTTCGTCATCTTGGACTCAGTAAA  
AGTGATTCTAGCAATAGTGATTCCACTCAGAGTCAGAAGTCTGGCAGGAACCTCGAACC  
CCCGCAAGCACGCAACTAAATCCCGAAATACAAAAAGTAACACAGTGGACTTCCTAT  
TAAGACTTACTTGCAATTGCTGGACTAGCAAAGGAAAATTGCACTATTGCACATCATATT  
CTATTGTTTACTATAAAAATCATGTGATAACTGATTATTACTTCTGTTTCTTTTGGTTT  
CTGCTTCTCTTCTCTCAACCCCTTGTAAATGGTTTGGGGGCAGACTCTTAAGTATATT  
GTGAGTTTCTATTTCACTAATCATGAGAAAACTGTTCTTTTGCAATAATAATAAATT  
AAACATGCTGTTA

Figure 84

MVCGSPGGMILLRAGLLALAALCLLRVPGARAAACEPVRIPLCKSLPWNMTKMPNHLHH  
STQANAILAIEQFEGLLGTHCSPDLLFFLCAMYAPICTIDFQHEPIKPKCSVCERARQGCEPIL  
IKYRHSWPENLACEELPVYDRGVCISPEAIVTADGADFPMDSSNGNCRGASSERCKCKPIR  
ATQKTYFRNNYNYVIRAKVKEIKTKCHDVTAVVEVKEILKSSLVNIPRDTVNLTYTSSGCLC  
PPLNVNEEYIIMGYEDEERSRLLLVEGSIAEKWKDRLGKKVKRWDMLRHLGLSKSDSSN  
SDSTQSQKSGRNSNPRQARN

Figure 85

CAGCGGCCGCTGAATTCTAGGGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGC  
TCGTGCCCTGTGTGCCAGACGGCGGAGCTCCGCGGCCGGACCCCGCGGCCCGCTTTG  
CTGCCGACTGGAGTTTGGGGGAAGAACTCTCCTGCGCCCCAGAAGATTTCTTCTCGG  
CGAAGGGACAGCGAAAGATGAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGG  
GGTCGCAGCGCGAGAGGGCAGTGCCATGTTCTCTCCATCCTAGTGGCGCTGTGCCTGT  
GGCTGCACCTGGCGCTGGGCGTGC CGCGCGGCCCTGCGAGGCGGTGCGCATCCCTAT  
GTGCCGGCACATGCCCTGGAACATCACGCGGATGCCCAACCACCTGCACCACAGCACG  
CAGGAGAACGCCATCCTGGCCATCGAGCAGTACGAGGAGCTGGTGGACGTGAACTGC  
AGCGCCGTGCTGCGCTTCTTCTTCTGTGCCATGTACGCGCCCATTTGCACCCTGGAGTT  
CCTGCACGACCTATCAAGCCGTGCAAGTCGGTGTGCCAACGCGCGCGGACGACTGC  
GAGCCCCCTCATGAAGATGTACAACCACAGCTGGCCCCGAAAGCCTGGCCTGCGACGAGC  
TGCTGTCTATGACCGTGGCGTGTGCATTTTCGCTGAAGCCATCGTCACGGACCTCCCG  
GAGGATGTTAAGTGGATAGACATCACACCAGACATGATGGTACAGGAAAGGCCTCTTG  
ATGTTGACTGTAAACGCCCTAAGCCCCGATCGGTGCAAGTGTA AAAAGGTGAAGCCAAC  
TTTGGCAACGTATCTCAGCAAAACTACAGCTATGTTATTATGCCAAAATAAAAGCTG  
TGCAGAGGAGTGGCTGCAATGAGGTCAACCGGTGGTGGATGTAAAAGAGATCTTCAA  
GTCCTCATCACCCATCCCTCGAACTCAAGTCCCGCTCATTACAAATTTCTTCTGCCAGT  
GTCCACACATCCTGCCCCATCAAGATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGG  
ATGATGCTTCTTGAAAATTGCTTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAAGAT  
CCATACAGTGGGAAGAGAGGCTGCAGGAACAGCGGAGAACAGTTACAGGACAAGAAGA  
AAACAGCCGGGCGCACCCAGTCGTAGTAATCCCCCAAACCAAAGGGAAAGCCTCCTGC  
TCCCAAACCCAGCCAGTCCCAAGAAGAACATTAAACTAGGAGTGCCCAAGAGAAAC  
AAACCCGAAAAGAGTGTGAGCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCCTTA  
CAGGATGAGGCTGGGCATTGCCTGGGACAGCCTATGTAAAGGCCATGTGCCCTTGCCC  
TAACAACTCACTGCAGTGCTCTTCATAGACACATCTTGCAGCATTTTTCTTAAGGCTAT  
GCTTCAGTTTTTTCTTTGTAAGCCATCACAAGCCATAGTGGTAGGTTTGCCCTTTGGTACA  
GAAGGTGAGTTAAAGCTGGTGGAAAAGGCTTATTGCATTGCATTACAGGTAACTGTG  
TGCATACTCTAGAAGAGTAGGGAAAATAATGCTTGTTACAATTCGACCTAATATGTGC  
ATTGTAAAATAAATGCCATATTTCAAACAAAACACGTAATTTTTTTACAGTATGTTTTA  
TTACCTTTTGATATCTGTTGTTGCAATGTTAGTGATGTTTTAAAATGTGATGAAAATATA  
ATGTTTTTAAGAAGGAACAGTAGTGGAATGAATGTAAAAGATCTTTATGTGTTTATGG  
TCTGCAGAAGGATTTTTGTGATGAAAGGGGATTTTTTGAAAAATTAGAGAAGTAGCAT  
ATGGAAAATTATAATGTGTTTTTTTACCAATGACTTCAGTTTTCTGTTTTTAGCTAGAAAC  
TTAAAAACAAAATAATAATAAGAAAAATAAATAAAAAGGAGAGGCAGACAATGTC  
TGGATTCTGTTTTTTGGTTACCTGATTTCCATGATCATGATGCTTCTTGTCAACACCCCT  
CTTAAGCAGCACCCAGAAACAGTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATTA  
GTTGGCTAATGCTCAAGTATTTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTC  
CCAGGACATCCACCCTGAGAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTG  
CCAAATTTTGTTTTTCTTCATTTAAATATTTCTTTGCCTAAATACATGTGAGAGGAGTT  
AAATATAAATGTACAGAGAGGAAAGTTGAGTTCCACCTCTGAAATGAGAATTACTTGA  
CAGTTGGGATACTTTAATCAGAAAAAAGAACTTATTTGCAGCATTTTATCAACAAAT  
TCTTATTTCTGAGCAATTTGACCGCATTTATTTTAAAAAACAATTTTATTGGCCTTTTGCT

AACACAGTAAGCATGTATTTTATAAGGCATTCAATAAATGCACAACGCCCAAAGGAAA  
TAAATCCTATCTAATCCTACTCTCCACTACACAGAGGTAATCACTATTAGTATTTTGG  
CATATTATTCTCCAGGTGTTTGCTTATGCACTTATAAAATGATTTGAACAAATAAACT  
AGGAACCTGTATACATGTGTTTCATAACCTGCCTCCTTTGCTTGGCCCTTTATTGAGATA  
AGTTTTCTGTCAAGAAAGCAGAAACCATCTCATTTCTAACAGCTGTGTTATATTCCAT  
AGTATGCATTACTCAACAACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGA  
CAATACTGAATAAACATCTCACCGGAATTC

Figure 86

MFLSILVALCLWLHLALGVRGAPCEAVRIPMCRHMPWNITRMPNHLHHSTQENAILAIEQY  
EELVDVNCSAVLRFFLCAMYAPICTLEFLHDPIKPKSVQQRARDDCEPLMKMYNHSWPE  
SLACDELPVYDRGVCISPEAIVTDLPEDVKWIDITPDMMVQERPLDVDCRRLSPDRCKCKK  
VKPTLATYLSKNYSYVIHAKIKAVQSRGCGNEVTTVVDVKEIFKSSSPIRPTQVPLITNSSCQC  
PHILPHQDVLIMCYEWRSRMMLLENCLVEKWRDQLSKRSIQWEERLQEQRRTVQDKKKK  
AGRTSRSNPPKPKGKPPAPKPASPKNKIKTRSAQKRTNPKRV

Figure 87

AAGCTTGATATCGAATTCGCGGCCGCGTCGACGGGAGGCGCCAGGATCAGTCGGGGCA  
CCCGCAGCGCAGGCTGCCACCCACCTGGGCGACCTCCGCGGCGGCGGCGGCGGCGGCT  
GGGTAGAGTCAGGGCCGGGGGCGCACGCCGAACACCTGGGCGCGCGGGCACCGAGC  
GTCGGGGGGGCTGCGCGGCGCGACCCCTGGAGAGGGCGCAGCCGATGCGGGCGGCGGCG  
GCGGCGGGGGGCGTGCGGACGGCCGCGCTGGCGCTGCTGCTGGGGGCGCTGCACTGG  
GCGCCGGCGCGCTGCGAGGAGTACGACTACTATGGCTGGCAGGCCGAGCCGCTGCACG  
GCCGCTCCTACTCCAAGCCGCCGCACTGCCTTGACATCCCTGCCGACCTGCCGCTCTGC  
CACACGGTGGGCTACAAGCGCATGCGGCTGCCAACCTGCTGGAGCACGAGAGCCTGG  
CCGAAGTGAAGCAGCAGGCGAGCAGCTGGCTGCCGCTGCTGGCCAAGCGCTGCCACTC  
GGATACGCAGGTCTTCCTGTGCTCGCTCTTTGCGCCCGTCTGTCTCGACCGGCCCATCT  
ACCCGTGCCGCTCGCTGTGCGAGGCCGTGCGCGCCGGCTGCGCGCCGCTCATGGAGGC  
CTACGGCTTCCCCTGGCCTGAGATGCTGCACTGCCACAAGTCCCCCTGGACAACGACC  
TCTGCATCGCCGTGCAGTTCGGGCACCTGCCCGCCACCGCGCCTCCAGTGACCAAGATC  
TGCGCCCAAGTGTGAGATGGAGCACAGTGCTGACGGCCTCATGGAGCAGATGTGCTCCA  
GTGACTTTGTGGTCAAAATGCGCATCAAGGAGATCAAGATAGAGAATGGGGACCGGA  
AGCTGATTGGAGCCCAGAAAAAGAAGAAGCTGCTCAAGCCGGGGCCCCCTGAAGCGCA  
AGGACACCAAGCGGCTGGTGCTGCACATGAAGAATGGCGCGGGCTGCCCTGCCACA  
GCTGGACAGCCTGGCGGGCAGCTTCCTGGTCATGGGCGCAAAGTGATGGACAGCTG  
CTGCTCATGGCCGTCTACCGCTGGGACAAGAAGAATAAGGAGATGAAGTTTGCAGTCA  
AATTCATGTTCTCCTACCCCTGCTCCCTCTACTACCTTTCTTCTACGGGGCGGCAGAGC  
CCCACTGAAGGGCACTCCTCCTTGCCCTGCCAGCTGTGCCTTGCTTGCCCTCTGGCCCC  
GCCCCAATTCCAGGCTGACCCGGCCCTACTGGAGGGTGTTCACGAATGTTGTTACT  
GGCACAAGGCCTAAGGGATGGGCACGGAGCCCAGGCTGTCCTTTTGACCCAGGGGTG  
CTGGGGTCCCTGGGATGTTGGGCTTCTCTCTCAGGAGCAGGGCTTCTTCATCTGGGTG  
AAGACCTCAGGGTCTCAGAAAGTAGGCAGGGGAGGAGAGGGTAAGGGAAAGGTGGAG  
GGGCTCAGGGCACCCCTGAGGCGGAGGTTTCAGAGTAGAAGGTGATGTCAGCTCCAGCT  
CCCCTCTGTGCGGTGGTGGGGCCTCACCTTGAAGAGGGAAGTCTCAATATTAGGCTAAG  
CTATTTGGGAAAGTTCTCCCCACCGCCCTGTACGCGTCATCCTAGCCCCCTTAGGAA  
AGGAGTTAGGGTCTCAGTGCTCCAGCCACACCCCTGCCTTCCCCAGCTTGCCCATTT  
CCCTGCCCCAAGGCCAGAGCTCCCCCAGACTGGAGAGCAAGCCCAGCCCAGCCTCG  
GCATAGACCCCTTCTGGTCCGCGCCGCTGGCTCGATTCCCGGGATTCAATCCTCAGCCTC

TGCTTCTCCCTTTTATCCCAATAAGTTATTGCTACTGCTGTGAGGCCATAGGTACTAGAC  
AACCAATACATGCAGGGTTGGGTTTTCTAATTTTTTAACTTTTTTAATTAAATCAAAGGT  
CGACGCGCGGCCGCGGAATTCCTGCAGCCCGGGGGATCCCCGGGTACCGAGCTCGAAT  
TC

Figure 88

TEILPALCVLIHHTDVNILDVTVWALSYLTDAGNEQIQMVIDSGIVPHLVPLLSHQEVKVQT  
AALRAVGNIVTGTDEQTQVVLNCDALSHFPALLTHPKEKINKEAVWFLSNITAGNQQQVQ  
AVIDANLVPMIHLDDKGDFTQKEAAWAISNLTISGRKDQVAYLIQQNVPPFCNLLTVKD  
AQVVQVVL DGLSNILKMAEDEAETIGNLIEECGGLEKIEQLQNHENEDIYKLAYEIIDQFFSS  
DDIDEDPSLVPEAIQGGTGFNSSANVPTEGFQF

Figure 89

ATGCATCTCCTCTTATTTTCAGCTGCTGGTACTCCTGCCTCTAGGAAAGACCACACGGCA  
CCAGGATGGCCGCCAGAATCAGAGTTCTCTTTCCCCCGTACTCCTGCCAAGGAATCAA  
AGAGAGCTTCCCACAGGCAACCATGAGGAAGCTGAGGAGAAGCCAGATCTGTTTGTGC  
CAGTGCCACACCTTGTAGCCACCAGCCCTGCAGGGGAAGGCCAGAGGCAGAGAGAGA  
AGATGCTGTCCAGATTTGGCAGGTTCTGGAAGAAGCCTGAGAGAGAAATGCATCCATC  
CAGGGACTCAGATAGTGAGCCCTTCCCACCTGGGACCCAGTCCCTCATCCAGCCGATA  
GATGGAATGAAAATGGAGAAATCTCCTCTTCGGGAAGAAGCCAAGAAATTCTGGCACC  
ACTTCATGTTTCAGAAAACTCCGGCTTCTCAGGGGGTCATCTTGCCCATCAAAAGCCAT  
GAAGTACATTGGGAGACCTGCAGGACAGTGCCCTTCAGCCAGACTATAACCCACGAAG  
GCTGTGAAAAAGTAGTTGTTTCAGAACACCTTTGCTTTGGGAAATGCGGGTCTGTTTCAT  
TTTCTTGAGCCGCGCAGCACTCCCATACTCCTGCTCTCACTGTTTGCCTGCCAAGTTC  
ACCACGATGCACTTGCCACTGAACTGCACTGAACTTTCCTCCGTGATCAAGGTGGTGAT  
GCTGGTGGAGGAGTGCCAGTGCAAGGTGAAGACGGAGCATGAAGATGGACACATCCT  
ACATGCTGGCTCCCAGGATTCTTTATCCCAGGAGTTTCAGCTTGA

Figure 90

MHLLLFQLLVLLPLGKTTRHQDGRQNQSSLSPVLLPRNQRELPTGNHEEAEEKPDLFVAVP  
HLVATSPAGEGQRQREKMLSRFGRFWKKPEREMHPSRSDSEPFPPGTQSLIQPIDGMKME  
KSPLREEAKKFWHFMRKTPASQGVILPIKSHEVHWETCRTVPFSQTTTIEGCEKVVVQN  
NLFCGKCGSVHFPGAAQHSHTSCSHCLPAKFTTMHLPLNCTELSSVIKVVMLVEECQCKV  
KTEHEDGHILHAGSQDSFIPGVSA

Figure 91

CGGCACGGTTTCGTGGGGACCCAGGCTTGCAAAGTGACGGTCATTTTCTCTTTCTTTCT  
CCCTCTTGAGTCCTTCTGAGATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTT  
GTCGCGATGGTAGCGGCGGCTCTCGGCGGCCACCCTCTGCTGGGAGTGAGCGCCACCT  
TGAACCTCGGTTCTCAATTCCAACGCTATCAAGAACCTGCCCCACCGCTGGGCGGCGCT  
GCGGGGCACCCAGGCTCTGCAGTCAGCGCCGCGCCGGGAATCCTGTACCCGGGCGGGA  
ATAAGTACCAGACCATTGACAACTACCAGCCGTACCCGTGCGCAGAGGACGAGGAGTG  
CGGCACTGATGAGTACTGCGCTAGTCCCACCCGCGGAGGGGACGCAGGCGTGCAAATC



GGAATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCAAAAATCATTTCGGAGGAGA  
AATTGAGGAAACCATCACTGAAAGCTTTGGTAATGATCATAGCACCTTGGATGGGTAT  
TCCAGAAGAACCACCTTGTCTTCAAAAATGTATCACACCAAAGGACAAGAAGGTTCTG  
TTTGTCTCCGGTCATCAGACTGTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCA  
AGATCTGTAAACCTGTCCTGAAAGAAGGTCAAGTGTGTACCAAGCATAGGAGAAAAGG  
CTCTCATGGACTAGAAATATTCCAGCGTTGTTACTGTGGAGAAGGTCTGTCTTGCCGGA  
TACAGAAAGATCACCATCAAGCCAGTAATTCTTCTAGGCTTCACACTTGTGAGAGACAC  
TAAACCAGCTATCCAAATGCAGTGAACCTCTTTATATAATAGATGCTATGAAAACCTT  
TTATGACCTTCATCAACTCAATCCTAAGGATATACAAGTTCTGTGGTTTCAGTTAAGCA  
TTCCAATAACACCTTCCAAAAACCTGGAGTGTAAGAGCTTTGTTTCTTTATGGAACCTC  
CCTGTGATTGCAGTAAATTACTGTATTGTAAATTCTCAGTGTGGCACTTACCTGTAAAT  
GCAATGAAACCTTTTAATTATTTTTCTAAAGGTGCTGCACTGCCTATTTTTCTCTTGTTA  
TGTAATTTTTGTACACATTGATTGTTATCTTGACTGACAAATATTCTATATTGAACTGA  
AGTAAATCATTTTCAGCTTATAGTTCTTAAAAGCATAACCCTTTACCCCATTTAATTCTAG  
AGTCTAGAACGCAAGGATCTCTTGGAATGACAAATGATAGGTACCTAAAATGTAACAT  
GAAAATACTAGCTTATTTTTCTGAAATGTACTATCTTAATGCTTAAATTATTTCCCTTT  
AGGCTGTGATAGTTTTTGAAATAAAATTTAACATTTAATATCATGAAATGTTATAAGTA  
GACAT

Figure 92

MMALGAAGATRVFVAMVAAALGGHPLLGVSATLNSVLNSNAIKNLPPPLGGAAGHPGSA  
VSAAPGILYPGGNKYQTIDNYQPYPCAEEDEECGTDEYCASPTRGGDAGVQICLACRKRK  
RCMRHAMCCPGNYCKNGICVSSDQNHFRGEIETITESFGNDHSTLDGYSRRITLSSKMYH  
TKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCG  
EGLSCRIQKDDHHQASNSSRLHTCQRH

Figure 93

GCGGGTCTCGCTTGGGTTCCGCTAATTTCTGTCTGAGGCGTGAGACTGAGTTCATAGG  
GTCCTGGGTCCCCGAACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCCGCGAC  
CCAAGTGAGGGGCCCCGTGTTGGGGTCTCCCTCCCTTTGCATTCCCACCCCTCCGGGC  
TTTGCGTCTTCTGCGGACCCCTCGCCGGGAGATGGCCGCGTTGATGCGGAGCAAGG  
ATTCGTCTGCTGCTGCTCCTACTGGCCGCGGTGCTGATGGTGGAGAGCTCACAGATC  
GGCAGTTCGCGGGCCAACTCAACTCCATCAAGTCCTCTCTGGGCGGGGAGACGCCTG  
GTCAGGCCGCCAATCGATCTGCGGGCATGTACCAAGGACTGGCATTGCGCGGCAGTAA  
GAAGGGCAAAAACCTGGGGCAGGCCTACCCTTGTAGCAGTGATAAGGAGTGTGAAGTT  
GGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCCTGCATGGTGTGTCGGAGAA  
AAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGCTGCAATAATGG  
CATCTGTATCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGGCTCTGGATGGTA  
CTCGGCACAGAGATCGAAACCACGGTCATTACTCAAACCATGACTTGGGATGGCAGAA  
TCTAGGAAGACCACACACTAAGATGTCACATATAAAAGGGCATGAAGGAGACCCCTGC  
CTACGATCATCAGACTGCATTGAAGGGTTTTGCTGTGCTCGTCATTCTGGACCAAAAT  
CTGCAAACCAGTGCTCCATCAGGGGGAAGTCTGTACCAAACAACGCAAGAAGGGTTCT  
CATGGGCTGGAAATTTTCCAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAAGTATG  
GAAAGATGCCACCTACTCCTCAAAGCCAGACTCCATGTGTGTCAGAAAATTTGATCA  
CCATTGAGGAACATCATCAATTGCAGACTGTGAAGTTGTGTATTTAATGCATTATAGCA  
TGGTGGAAAATAAGGTTTCAGATGCAGAAGAATGGCTAAAATAAGAAACGTGATAAGA  
ATATAGATGATCAC

Figure 94

MAALMRSKDSCLLLLA VLMVESSQIGSSRAKLNSIKSSLGGETPGQAANRSAGMYQG  
LAFGGSKKGKNLGQAYPCSSDKECEVGRYCHSPHQSSACMVCRRKKKRCHRDGMCCPS  
TRCNNGICIPVTESILTPHIPALDGTRHRDRNHGHYSNHD LGWQNLGRPHTKMSHIKGHEG  
DPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGSHGLEIFQRCDCAKGLSCKV  
WKDATYSSKARLHVCQKI

Figure 95

CTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCAC  
CGAGAAATTCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAG  
TTATCACATCTGTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACG  
AGGACTGTGGGCCAGCATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGCC  
ATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACAGTGAGTGCTGTGGAGACCAGCTG  
TGTGTCTGGGGTCACTGCACCAAAATGGCCACCAGGGGCAGCAATGGGACCATCTGTG  
ACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCTTCCAGAGAGGCCTGCTGTT  
CCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACCCCGCCAGCCGG  
CTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGATGCCCTTG  
TGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGCCG  
ACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTCCCCG  
ATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGA  
GAGGAGCCTGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTG  
CTGGGAGGGGAAGAGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAAT  
AGCTAATTTATTTCCCCAGGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCTAC  
ATCTTCTTCCAGTAAGTTTCCCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTT  
AGCTCCCCCAGGCTGTTCTCCAGGCTTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGG  
GTAAACTGCAGGAGCAGTTTGCCACCCCTGTCCAGATTATTGGCTGCTTTGCCTCTAC  
CAGTTGGCAGACAGCCGTTTGTCTACATGGCTTTGATAATTGTTTGAGGGGAGGAGAT  
GGAAACAATGTGGAGTCTCCCTCTGATTGTTTTGGGGAAATGTGGAGAAGAGTGCCC  
TGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAATGAATTTTCCACGCAGTTCTTT  
CCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGTTCTGTTCACCTT  
GCATTACATGTGTTTATTCATCCAGCAGTGTGCTCAGCTCCTACCTCTGTGCCAGGGC  
AGCATTTTCATATCCAAGATCAATTCCCTCTCTCAGCACAGCCTGGGGAGGGGGTTCATT  
GTTCTCCTCGTCCATCAGGGATCTCAGAGGNCTCAGAGACTGCAAGCTGCTTGCCCAA  
GTCACACAGCTAGTGAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGC  
TCTCTCCACTACCCACACCAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGG  
AGAATGGGATTTTTCTTTTGAGGCATGCACATCTGGAATTAAGGTCAAATAATTCTCA  
CATCCCTCTAAAAGTAACTACTGTTAGGAACAGCAGTGTCTCACAGTGTGGGGCAG  
CCGTCCTTCTAATGAAGACAATGATATTGACACTGTCCCTCTTTGGCAGTTGCATTAGT  
AACTTTGAAAGGTATATGACTGAGCGTAGCATAACAGTTAACCTGCAGAAACAGTACT  
TAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAATCACTTAGCAGCAACT  
GAAGACAATTATCAACCACGTGGAGAAAAATCAAACCGAGCAGGGCTGTGTGAAACAT  
GGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAATGATGTTTTCA  
GGTGTGATGACTGTTGCCACCATGTATTCATCCAGAGTTCTTAAAGTTTAAAGTTGCA  
CATGATTGTATAAGCATGCTTTCTTTGAGTTTTTAAATTATGTATAAACATAAGTTGCATT  
TAGAAATCAAGCATAAATCAC



Figure 96

MQRLGATLLCLLLAAAVPTAPAPAPTATSAPVKPGPALSYQEEATLNEMFREVEELMEDT  
QHKLRSAVEEMEAEEAAAKASSEVNLANLPPSYHNETNTDTKVGNNTIHVHREIHKITNNQ  
TGQMVFSETVITSVGDEEGRRSHECIIDEDCGPSMYCQFASFQYTCQPCRQGRMLCTRDSE  
CCGDQLCVWGHCTKMATRGSNGTICDNQRDCQPLCCAFQRGLLFPVCTPLPVEGELCHD  
PASRLDLITWELEPDGALDRPCASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILLPREVP  
DEYEVGSFMEEVRQELEDLERSLTEEMALGEPAAAAAALLGGBEI

Figure 97

AGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGAGCAGCCT  
CGCTTTGGTGACGCACAGTGCTGGGACCCTCCAGGAGCCCCGGGATTGAAGGATGGTG  
GCGGCCGTCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGGTCCTGGA  
CTTCAACAACATCAGGAGCTCTGCTGACCTGCATGGGGCCCCGGAAGGGCTCACAGTGC  
CTGTCTGACACGGACTGCAATACCAGAAAGTTCTGCCTCCAGCCCCGCGATGAGAAGC  
CGTTCTGTGCTACATGTCGTGGGTTGCGGAGGAGGTGCCAGCGAGATGCCATGTGCTG  
CCCTGGGACACTCTGTGTGAACGATGTTTGTACTACGATGGAAGATGCAACCCCAATAT  
TAGAAAGGCAGCTTGATGAGCAAGATGGCACACATGCAGAAGGAACAACCTGGGCACC  
CAGTCCAGGAAAACCAACCCAAAAGGAAGCCAAGTATTAAGAAATCACAAGGCAGGA  
AGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTTACTGTGGCCCTGGACTTTGCTG  
TGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAGGGACAGGTCTGCT  
CCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGTTGCGACTG  
TGGCCCTGGACTACTGTGTGCGAAGCCAATTGACCAGCAATCGGCAGCATGCTCGATTA  
AGAGTATGCCAAAAAATAGAAAAGCTATAAATATTTCAAATAAAGAAGAATCCACAT  
TGC

Figure 98

MVA AVLGLSWLCSPLGALVLD FNNIRSSADLHGARKGSQCLSDTDCNTRKFCLQPRDEK  
PFCATCRGLRRRCQRDAMCCPGTLCVNDVCTT MEDATPILERQLDEQDGHAE GTTGHPV  
QENQPKRKPSIKKSQGRKGQEGESCLRTFDCGPG LCCARHFWTKICKPVLLEGQVCSRRGH  
KDTAQAPEIFQRCD CGPGLLCRSQ LTSNRQHARLRVCQKIEKL

Figure 99

AGGCAGAATACTTCTATGAATTCCTGTCTTGCCTCCCTGGATAAAGGCATCATGGCA  
GATCCAACCGTCAATGTCCCTCTGCTGGGAACAGTGCCTCACAAGGCATCAGTTGTTCA  
AGTTGGTTTCCCATGTCTTGGAAAACAGGATGGGGTGGCAGCATTTGAAGTGGATGTG  
ATTGTTATGAATTCTGAAGGCAACACCATTCTCCAAACACCTCAAAATGCTATCTTCTT  
TAAAACATGTCAACAAGCTGAGTGCCAGGCGGGTGCCGAAATGGAGGCTTTTGTAAAT  
GAAAGACGCATCTGCGAGTGTCTGATGGGTTCCACGGACCTCACTGTGAGAAAGCCC  
TTTGTACCCACGATGTATGAATGGTGGACTTTGTGTGACTCCTGGTTTCTGCATCTGCC  
CACCTGGATTCTATGGAGTGAACGTGTGACAAAGCAAACCTGCTCAACCACCTGCTTTAAT  
-----TGGGCGCAAAATGCTATTTTCCCTCCAGGACTAGAGGGAGAGC

AGTGTGAAATCAGCAAATGCCCACAACCCTGTCGAAATGGAGGTAAATGCATTGGTAA  
AAGCAAATGTAAGTGTTCAAAGGTTACCAGGGAGACCTCTGTTCAAAGCCTGTCTGC  
GAGCCTGGCTGTGGTGCACATGGAACCTGCCATGAACCCAACAAATGCCAATGTCAAG  
AAGGTTGGCATGGAAGACACTGCAATAAAAGGTACGAAGCCAGCCTCATAATGCCCT  
GAGCGCAGCAGCGCCCAGCTCAGGCAGCACACGCCTTCACTTAAAAAGGCCGAGGAG  
CGGCGGCATCCACCTGAATCCAATTACATCTGGTGAACCTCCGACATCTGAAACGTTTTA  
AGTTACACCAAGTTCATAGCCTTTGTAAACCTTTTCATGTGTTGAATGTTCAAATAATGTT  
CATTACACTTAAGAATACTGGCCTGAATTTTATTAGCTTCATTATAAATCACTGAGCTG  
ATATTTACTCTTCCTTTTAAGTTTTCTAAGTACGTCTGTAGCATGATGGTATAGATTTTC  
TTGTTTCAGTGCTTTGGGACAGATTTTATATTATGTCAATTGATCAGGTTAAAATTTTCA  
GTGTGTAGTTGGCAGATAATTTCAAATTACAATGCATTTATGGTGTCTGGGGGCAGGG  
GAACATCAGAAAGGTTAAATTGGGCAAAAATGCGTAAAGTCACAAGAATTTGGATGGTG  
CAGTTAATGTTGAAGTTACAGCATTTTCAGATTTTATTGTGAGATATTTAGATGTTTGTGA  
CATTTTTAAAAATTGCTCTTAATTTTTTAAACTCTCAATACAATATATTTTGACCTTACCA  
TTATTCCAGAGATTCAGTATTAATAAAAAAAAAAATTACACTGTGGTAGTGGCATTAA  
ACAATATAATATATTCTAAACACAATGAAATAGGGAATATAATGTATGAACTTTTTGCA  
TTGGCTTGAAGCAATATAATATATTGTAAACAAAACACAGCTCTTACCTAATAAACATT  
TTATACTGTTTGTATGTATAAAATAAAGGTGCTGCTTTAGTTTTTC

Figure 100

MARRSAFPAAALWLWSILLCLLALRAEAGPPQEESELYLWIDAHQARVLIGFEEDILIVSEK  
MAPFTHDFRKAQQRMPAIPVNIHSMNFTWQAAGQAEYFYEFSLRSLDKGIMADPTVNP  
LLGTVPHKASVVQVGFPCLGKQDGVAAFEVDVIVMNSEGNILQTPQNAIFFKTCLEACP  
GGCRNGGFCNERRICECPDGFHGPHEKALCTPRCMNGGLCVTPGFICPPGFYGVNCDK  
ANCSTTCFNGGTCTFYPGKCICPPGLEGEQCEISKCPQPCRNGGKCIGKSKCKCSKGYQGD  
CSKPVCEPGCAHGTCHPNKCQCQEGWHGRHCNKRYEASLIHALR  
PAGAQLRQHTPSLKKAEBRRDPPESENYTW

Figure 101

ATGGGCATCGGGCGCAGCGAGGGGGGCGCGCGGGGCAGCCCTGGGCGTGCTGCTG  
GCGCTGGGCGCGGCGCTTCTGGCCGTGGGCTCGGCCAGCGAGTACGACTACGTGAGCT  
TCCAGTCGGACATCGGCCCGTACCAGAGCGGGCGCTTCTACACCAAGCCACCTCAGTG  
CGTGGACATCCCCGCGGACCTGCGGCTGTGCCACAACGTGGGCTACAAGAAGATGGTG  
CTGCCCAACCTGCTGGAGCACGAGACCATGGCGGAGGTGAAGCAGCAGGCCAGCAGC  
TGGGTGCCCTGCTCAACAAGAACTGCCACGCCGGCACCCAGGTCTTCTCTGCTCGCT  
CTTCGCGCCCGTCTGCCCTGGACCGGCCCATCTACCCGTGTCGCTGGCTCTGCGAGGCCG  
TGCGCGACTCGTGCGAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGCCCGAGATGCTT  
AAGTGTGACAAAGTTCCCCGAGGGGGACGTCTGCATCGCCATGACGCCGCCCAATGCCA  
CCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCCTCCCTGTGACAACGAGTTGAA  
ATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGGGCTGAGTTTAAAGATGA  
TTGTGGGTAGCTCCATAACTCATGCTGCACGCTGGGTCTTCTCATCCCAACTCCTCA  
AAGCGGCAGGAGCAGGAAGTGGGACTCCTGAGAGAAGGCTTGGATATGGCCTTTTAT  
TACACTTCATCCAAGGAAATCTGCCCCACCCTGTGCCAGGCCCGATCACGCATGAG  
GCTAAAGACGGAGGCCACTCCGCTGGCTCTGGGTAGATCTGCCCTGGACTGTTTGCC  
GACTGCCCGGAGCGCCCTCTGCCGGTCTGCAGCTTCCCACACCACACGGAAGAAGTGG  
GGAAACTGAGGATACATTCTTTCCTCCTCCAGGTAAAGGGATTCTCAATGAAGGGCTTG  
TGTGCACCTTCCACACTTAGATACCTCTACTACCTGAAAACCAGCATGCAGCATGTACA  
TCAAGAGTACCAGGCACATAGTGCTCAAGTCTGGGCTAATATGCCACCTGCAGAGAGA  
TCTTACATCAAGACACAAAGCCATGTTTTCAAAGTGA

Figure 102

MGIGRSEGGRRGAALGVLLALGAALLAVGSASEYDYVSFQSDIGPYQSGRFYTKPPQCVDI  
PADLRLCHNVGYKKMVLPLNLEHETMAEVKQQASSWVPLLKNKNCHAGTQVFLCSLFAPV  
CLDRPIYPCRWLCEAVRDSCEPVMQFFGFYWPEMLKCDKFPEGDVCIAMTPPNATEASKP  
QGTTVCPPCDNELKSEAIIEHLCASEFGLSLKMIVGSSHNSCCTLGPSHPNSSKRQEQELGTP  
ERRLGYGILLHFIQGNLPPCAQARSRLKTEATPLALGRSAPGLFADCPERPLPVCSPFH  
HTBEVGKLRHSFLLQVKGFMSMKGLCAPSTLRYLYLKTSMQHVHQEYQAHS AQVWANM  
PPAERCKDEEDKAMFSK

Figure 103

GGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGCTCGTGCCCTGTGTGCCAGAC  
GGCGGAGCTCCGCGGCCGACCCCGCGGCCCGCTTTGCTGCCGACTGGAGTTTGGGG  
GAAGAACTCTCCTGCGCCCCAGAAGATTTCTTCCTCGGCGAAGGGACAGCGAAAGAT  
GAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGGGGTCGCAGCGCGAGAGGGC  
AGTGCCATGTTCTCTCCATCCTAGTGGCGCTGTGCCTGTGGCTGCACCTGGCGCTGGG  
CGTGCGCGGCGCGCCCTGCGAGGCGGTGCGCATCCCTATGTGCCGGCACATGCCCTGG  
AACATCACGCGGATGCCCAACCACCTGCACCACAGCACGCAGGAGAACGCCATCCTGG  
CCATCGAGCAGTACGAGGAGCTGGTGGACGTGAACTGCAGCGCCGTGCTGCGCTTCTT  
CTTCTGTGCCATGTACGCGCCCATTTGCACCCTGGAGTTCCTGCACGACCCTATCAAGC  
CGTGCAAGTCGGTGTGCCAACGCGCGCGCGACGACTGCGAGCCCCCTCATGAAGATGTA  
CAACCACAGCTGGCCCCGAAAGCCTGGCCTGCGACGAGCTGCCTGTCTATGACCGTGGC  
GTGTGCATTTTCGCTGAAGCCATCGTCACGGACCTCCCGGAGGATGTTAGTGGATAGA  
CATCACACCAGACATGATGGTACAGGAAAGGCCTCTTGATGTTGACTGTAAACGCCTA  
AGCCCCGATCGGTGCAAGTGTA AAAAGGTGAAGCCAACCTTTGGCAACGTATCTCAGCA  
AAACTACAGCTATGTTATTCATGCCAAAATAAAAAGCTGTGCAGAGGAGTGGCTGCAA  
TGAGGTCACAACGGTGGTGGATGTAAAAGAGATCTTCAAGTCCTCATCACCCATCCCTC  
GAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGTGTCCACACATCCTGCCCCAT  
CAAGATGTTCTCATCATGTGTACGAGTGGCGTTCAAGGATGATGCTTCTTGAAAATTG  
CTTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAAGATCCATACAGTGGGAAGAGAG  
GCTGCAGGAACAGCGGAGAACAGTTCAGGACAAGAAGAAAACAGCCGGGCGCACCAG  
TCGTAGTAATCCCCCAAACCAAAGGGAAAGCCTCCTGCTCCCAAACCAGCCAGTCCC  
AAGAAGAACATTAAAACTAGGAGTGCCCGAGAAGAGAACAAACCCGAAAAGAGTGTGA  
GCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCCTTACAGGATGAGGCTGGGCATTG  
CCTGGGACAGCCTATGTAAGGCCATGTGCCCTTGCCCTAACAACTCACTGCAGTGCTC  
TTCATAGACACATCTTGCAGCATTTTTCTTAAGGCTATGCTTCAGTTTTTTCTTTGTAAGC  
CATCACAAGCCATAGTGGTAGGTTTGCCCTTTGGTACAGAAGGTGAGTTAAAGCTGGT  
GGAAAAGGCTTATTGCATTGCATTACAGTAACCTGTGTGCATACTCTAGAAGAGTAG  
GGAAAATAATGCTTGTTACAATTCGACCTAATATGTGCATTGTAAAATAAATGCCATAT  
TTCAAACAAAACACGTAATTTTTTTACAGTATGTTTTATTACCTTTTGATATCTGTTGTT  
GCAATGTTAGTGATGTTTTTAAAATGTGATGAAAATATAATGTTTTTAAGAAGGAACAGT  
AGTGGAAATGAATGTAAAAGATCTTTATGTGTTTATGGTCTGCAGAAGGATTTTTGTGA  
TGAAAGGGGATTTTTTGAAAAATTAGAGAAGTAGCATATGGAAAATTATAATGTGTTT  
TTTTACCAATGACTTCAGTTTCTGTTTTTAGCTAGAACTTAAAAACAAAATAATAAT  
AAAGAAAAATAAATAAAAAGGAGAGGCAGACAATGTCTGGATTCCTGTTTTTTGGTTA

CCTGATTTCCATGATCATGATGCTTCTTGTCAACACCCTCTTAAGCAGCACCAGAAACA  
GTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATTAGTTGGCTAATGCTCAAGT  
ATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTCCCAGGACATCCACCCTGA  
GAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTGCCAAATTTTGTTCCTTC  
ATTTAAATATTTTCTTTCCTAAATACATGTGAGAGGAGTTAAATATAAATGTACAGAG  
AGGAAAGTTGAGTTCCACCTCTGAAATGAGAATTACTTGACAGTTGGGATACTTTAATC  
AGAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATTTTATAATTGTGGACAATTG  
GAGGCATTTATTTTAAAAACAATTTTATTGGCCTTTTGCTAACACAGTAAGCATGTAT  
TTTATAAGGCATTCAATAAATGCACAACGCCCAAAGGAAATAAAATCCTATCTAATCC  
TACTCTCCACTACACAGAGGTAATCACTATTAGTATTTTGGCATATTATTCTCCAGGTGT  
TTGCTTATGCACTTATAAAATGATTTGAACAAATAAACTAGGAACCTGTATACATGTG  
TTTCATAACCTGCCTCCTTTGCTTGGCCCTTTATTGAGATAAGTTTTCTGTCAAGAAAG  
CAGAAACCATCTCATTCTAACAGCTGTGTTATATTCCATAGTATGCATTACTCAACAA  
ACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGACAATACTGAATAAACATCT  
CACCGGAATTC

Figure 104

MFLSILVALCLWLHLALGVRGAPCEAVRIPMCRHMPWNITRMPNHLHHSTQENAILAIEQY  
EELVDVNCSAVLRFFFCAMYAPICTLEFLHDPKPKSVQQRARDDCEPLMKMYNHSWPES  
LACDELPVYDRGVCISPEAIVTDLPEDVKWIDITPDMMVQERPLDVCKRLSPDRCKCKKV  
KPTLATYLSKNYSYVIHAKIKAVQRSGCNEVTTVVDVKEIFKSSSPIRTQVPLITNSSCQCP  
HILPHQDVLIMCYEWRSRMMLLENCLVEKWRDQLSKRSIQWEERLQEQRRTVQDKKKT  
GRTSRSNPPKPKGKPPAPKPASPKNKTRSAQKRTNPKRV

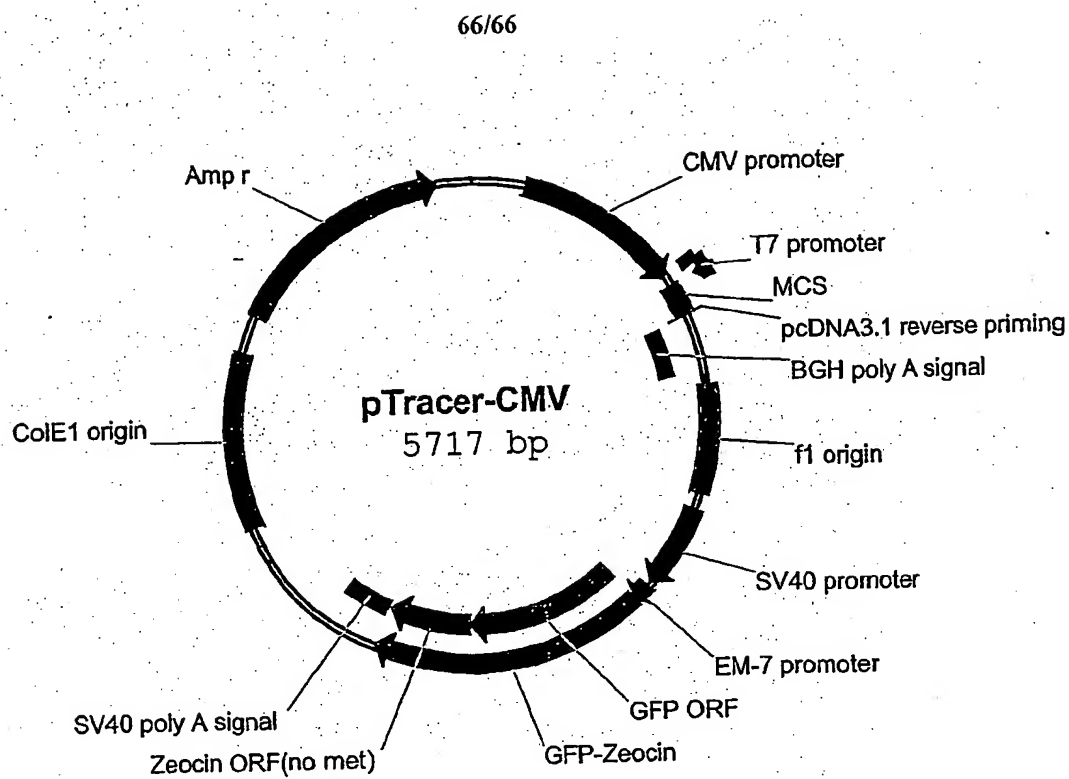


Figure 105

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(71) Applicant (*for all designated States except US*): AXORDIA LIMITED [GB/GB]; Firth Court, Western Bank, Sheffield S10 2TN (GB).

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(72) Inventors; and

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(74) Agent: HARRISON GODDARD FOOTE; 31 St. Saviourgate, York YO1 8NQ (GB).

(54) Title: STEM CELL DIFFERENTIATION

(57) Abstract: There is provided a method to modulate the differentiation state of embryonic stem cells in culture by the providing

WO 02/077204 A3

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 02/01195

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N5/06 C12N15/63

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBL, EPO-Internal, WPI Data, PAJ, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WAKEMAN JANE A ET AL: "Human Wnt-13 is developmentally regulated during the differentiation of NTERA-2 pluripotent human embryonal carcinoma cells."</p> <p>ONCOGENE, vol. 17, no. 2, 16 July 1998 (1998-07-16), pages 179-186, XP002216009 ISSN: 0950-9232 page 184, right-hand column, paragraph 1</p> <p>---</p> <p>-/--</p>	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

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Authorized officer

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SMOLICH BEVERLY D ET AL: "Regulated expression of Wnt family members during neuroectodermal differentiation of P19 embryonal carcinoma cells: Overexpression of Wnt-1 perturbs normal differentiation-specific properties." DEVELOPMENTAL BIOLOGY, vol. 166, no. 1, 1994, pages 300-310, XP002216010 ISSN: 0012-1606 abstract</p>	1
A	<p>LIU TONG ET AL: "Activation of rat Frizzled-1 promotes Wnt signaling and differentiation of mouse F9 teratocarcinoma cells via pathways that require G<math>\alpha</math>q and G<math>\alpha</math>o function." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 47, 19 November 1999 (1999-11-19), pages 33539-33544, XP002216011 ISSN: 0021-9258 abstract</p>	1
A	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2000 (2000-11-16) LAKO MAJLINDA ET AL: "Involvement of Wnt genes in early haematopoiesis and identification of Wnt3 as a regulator of haematopoietic commitment." Database accession no. PREV200100290162 XP002216012 abstract &amp; BLOOD, vol. 96, no. 11 Part 2, 16 November 2000 (2000-11-16), page 133b 42nd Annual Meeting of the American Society of Hematology; San Francisco, California, USA; December 01-05, 2000 ISSN: 0006-4971</p>	1
A	<p>US 5 780 300 A (ARTAVANIS-TSAKONAS SPYRIDON ET AL) 14 July 1998 (1998-07-14) the whole document</p>	1



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 02/01195

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 7, 12, 13, 22-26 all partially, 2 and 4 completely

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

The claims of the present application relate to methods for modulating and/or inhibiting embryonic stem cell differentiation by adding a ligand or a Wnt inhibitor to the culture or by coculture with cells which have been transfected with a nucleic acid encoding such a ligand or such a Wnt inhibitor.

However, the application only discloses the differential gene expression of a limited number of genes upon retinoic acid induced in vitro differentiation of an embryonal carcinoma cell line. No modulation of differentiation of embryonic stem cells is shown by any of the claimed methods.

Hence, the application provides neither support within the meaning of Article 6 PCT nor disclosure within the meaning of Article 5 PCT for any of the claimed subject matter. A meaningful search over the claimed scope is thus impossible.

Consequently, no search has been carried out for the present set of claims.

The applicant's attention is drawn to the fact that the same objection will arise for all the additional, non-unified inventions defined under the non-unity objection raised in the communication pursuant to Article 17(3)(a) PCT.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1, 7, 12, 13,  
22-26 all partially, 2 and 4 completely

Methods to modulate embryonic stem cell differentiation by providing a ligand to the culture, the ligand being human Wnt13

Inventions 2-23: claims 1, 3, 5-7, 12, 13,  
22-26 all partially

As invention 1 the ligand being WNT-1, WNT-2, WNT2B, WNT3, WNT4, WNT5A, WNT6, WNT7A, WNT8B, WNT10B, WNT11, WNT14, WNT16, murine notch ligand delta-like (DLL)1, murine notch ligand jagged (JAG)1, human JAG1, human JAG2, murine JAG2, human DLL3, human DLL1, human DLL4, and murine DLL4 respectively.

Inventions 24-32 : Claims 8, 12-15,  
22-26 all partially

Methods to modulate embryonic stem cell differentiation by coculturing with cells transfected with a ligand, the ligand being murine notch ligand delta-like (DLL)1, murine notch ligand jagged (JAG)1, human JAG1, human JAG2, murine JAG2, human DLL3, human DLL1, human DLL4, and murine DLL4 respectively.

Invention 33: Claims 9-11 completely, 12-15,  
22-26 all partially

Methods to modulate embryonic stem cell differentiation by coculturing with cells transfected with a ligand, the ligand being human Wnt13.

Inventions 34-57: Claims 16-18, 22,  
26 all partially

Methods to inhibit embryonic stem cell differentiation by providing a Wnt inhibitor to the culture, the Wnt inhibitor being frizzled (FZD)1, FZD2, FZE3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, frizzled related protein (FRP), SARP1, SARP2, FRZB, FRPHE, SARP3, cerberus (CER)1, dickkopf (DKK)1, DKK2, DKK3, DKK4, Wnt inhibitory factor (WIF)-1, SRFP1, and

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

SRFP4 respectively.

Inventions 58-82: Claims 19-22, 26 all partially

Methods to inhibit embryonic stem cell differentiation by coculturing with cells transfected with a Wnt inhibitor, the Wnt inhibitor being frizzled (FZD)1, FZD2, FZE3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, frizzled related protein (FRP), SARP1, SARP2, FRZB, FRPHE, SARP3, cerberus (CER)1, dickkopf (DKK)1, DKK2, DKK3, DKK4, Wnt inhibitory factor (WIF)-1, SRFP1, and SRFP4 respectively.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/GB 02/01195

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5780300	A	14-07-1998	
		AU 732629 B2	26-04-2001
		AU 7264996 A	17-04-1997
		CA 2233534 A1	03-04-1997
		EP 0948348 A1	13-10-1999
		JP 2000511043 T	29-08-2000
		WO 9711716 A1	03-04-1997
		US 6149902 A	21-11-2000
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